Tampere University

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Diagnosis, Risk Factors and Prevention of Periprosthetic Joint Infections

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The Road goes ever on and on
Down from the door where it began.
Now far ahead the Road has gone,
And I must follow, if I can.

- J.R.R. Tolkien, *The Fellowship of the Ring*

ABSTRACT

Periprosthetic joint infection (PJI) is a disastrous complication of joint replacement surgery, and approximately 1–2% of replaced joints become infected over the years. PJIs are associated with increased morbidity and mortality and treatment is costly. Because of this, PJIs are part of most surgical site infection surveillance programs and considerable efforts are made to prevent them. Nevertheless, there is still no uniform definition for PJI and existing definitions are based on a varied level of evidence. In addition, the usefulness of some of the methods used to prevent PJIs, such as screening for preoperative bacteriuria, has been questioned. On the other hand, there is a continuing search to identify new methods to prevent PJIs.

PJIs can be classified based on their timing with respect to previous surgery into early, delayed and late infections. Most of the late infections are hematogenous in origin, even though hematogenous PJIs can occur any time after surgery. Previous studies have shown that approximately one third of patients with *Staphylococcus aureus* bacteremia and a joint replacement develop a PJI, but little is known about the risk for other pathogens. Furthermore, the risk factors for developing a PJI during bacteremia are not known.

The present study examines two different diagnostic criteria sets used to identify PJIs and potential risk factors and ways of preventing PJIs, with an added emphasis on hematogenous PJIs. Data sources to identify PJIs were microbiological results, hospital discharge records and revision surgeries done because of an infection and the hospital's own infection records, in addition to prospectively collected infection surveillance data. Multiple data sources were used to identify PJIs as extensively as possible, especially late PJIs that are not identified by routine infection surveillance.

In a one-year follow-up after primary hip or knee replacement surgery, the incidence of PJI was 0.68% (158/23 171). The incidence was lower for hip replacements than for knee replacements: 0.57% vs. 0.77%. In the longer follow-up period (up to 12 years) the incidence of PJI after primary joint replacement surgery was 1.50% and the incidence rate was 3.3 per 1000 person-years.

Of the identified 405 PJI cases that met either one or both of the diagnostic criteria sets for PJI, 73 (18%) of the patients fulfilled only the older criteria, whereas only one (0.2%) fulfilled only the new criteria. Both sets of criteria were met by 331

(82%) of the patients. The diagnosis of PJI was based only on the clinician's opinion in 39 (53%) of the cases not meeting the new criteria set.

Of the previously reported risk factors for PJI, male gender (OR 2.21, 95% CI 1.56–3.11), knee replacement (OR 1.43, 95% CI 1.01–2.04) and older age (OR 1.03, 95% CI 1.01–1.05) were associated with an increased risk for PJI in a multivariable analysis, and the effect of diabetes was also almost statistically significant (OR 1.64, 95% CI 0.99–2.73).

On the other hand, preoperative bacteriuria was not associated with an increased risk for PJI in the univariate (OR 0.72, 95% CI 0.34–1.54) or multivariable analysis (OR 0.82, 95% CI 0.38–1.77). Furthermore, there was no correlation between the pathogens identified in the preoperative urine culture and those causing the PJIs, and treating the bacteriuria with effective antibiotics did not decrease the risk for developing a PJI (OR 0.62, 95% CI 0.07–5.14). Instead, the overall use of oral antibiotics preoperatively was associated with a decreased risk for developing a PJI (OR 0.40, 95% CI 0.22–0.73). In addition, the use of preoperative oral antibiotics was common, with 4106 (18%) joint replacement operations preceded by one or more courses of antibiotics.

During the follow-up of up to 12 years, 542 patients with a joint replacement (out of 14 378, 3.8%) developed at least one episode of bacteremia and 85 patients had multiple bacteremias. In total, there were 643 episodes of bacteremia. The most common pathogen causing the bacteremias was *Escherichia coli* (241/643, 37%). A PJI as a consequence of bacteremia developed in 7.2% of the bacteremias (46/643). This was most common for beta-hemolytic streptococci (21%, 12/58), *S.aureus* (20%, 21/105) and viridans group streptococci (16%, 4/25), but rare for gram-negative bacteria (1.3%, 4/314). There were no PJIs related to bacteremias caused by coagulase-negative staphylococci. Multiple bacteremias increased the risk for developing a PJI during bacteremia (OR 2.29, 95% CI 1.17–4.50) and the highest risk was for bacteremias occurring within one year from previous surgery. On the other hand, chronic diseases or other patient related factors did not influence the risk of developing a PJI as a consequence of bacteremia.

In conclusion, the different diagnostic criteria used to identify PJIs, especially in surgical site infection surveillance and research work, are not concordant with each other. The new, more objective, criteria produce notably lower number of PJIs that are identified. On the other hand, a large proportion of cases defined as infected by the treating clinician, did not meet the new criteria. There is still a lack of a gold standard to identify PJIs, especially in research and surveillance.

Based on the results of the study, preoperative urinary screening of asymptomatic patients before elective joint replacement surgery is not necessary to prevent PJIs, nor is treatment of asymptomatic preoperative bacteriuria. The lower risk of developing a PJI associated with preoperative oral antibiotic use is a novel finding and warrants further research before any definitive conclusions can be made on its significance. In addition, no modifiable patient-related risk factors could be identified to prevent the occurrence of a PJI as a consequence of bacteremia. However, the pathogen causing the bacteremia, previous history of infections and the timing of the bacteremia with respect to previous surgery should be taken into account when considering the risk for developing a PJI during bacteremia.

TIIVISTELMÄ

Tekonivelinfektio on tekonivelleikkauksen pelätyimpiä komplikaatioita, sillä niihin liittyy merkittävää sairastavuutta ja kuolleisuutta. Hoito on lisäksi kallista. Noin 1–2% tekonivelistä infektoituu. Näiden syiden vuoksi tekonivelinfektioita seurataan useimmissa hoitoon liittyvien infektioiden seurantaohjelmissa ja niiden ehkäisyyn käytetään merkittävästi resursseja. Tästä huolimatta tekonivelinfektiolle ei ole olemassa yhtenäistä määritelmää ja olemassa olevat määritelmät pohjautuvat vaihtelevaan näyttöön. Lisäksi joidenkin tekonivelinfektoiden ehkäisyssä käytettyjen menetelmien, kuten leikkausta edeltävän virtsanäytteen seulonnan, merkitys on kyseenalaistettu. Toisaalta uusia keinoja ehkäistä tekonivelinfektioita etsitään jatkuvasti.

Tekonivelinfektiot voidaan jakaa esiintymisajankohdan mukaan varhaisiin, viivästyneisiin ja myöhäisiin infektioihin. Suurin osa myöhäisistä infektioista on hematogeenisia, eli veriteitse levinneitä, mutta hematogeeninen tekonivelinfektio voi kehittyä missä vaiheessa vain leikkauksen jälkeen. Aiemmat tutkimukset ovat osoittaneet, että noin kolmasosa *Staphylococcus aureus*-bakteremioista johtaa tekonivelinfektioon potilailla, joilla on tekonivel, mutta muiden patogeenien osalta asiaa ei ole juuri tutkittu. Lisäksi riskitekijöitä tekonivelinfektion kehittymiselle bakteremian seurauksena ei tunneta.

Tässä tutkimuksessa verrataan kahta eri tekonivelinfektion määritelmää tekonivelinfektion diagnosoinnissa ja lisäksi tekonivelinfektion riskitekijöitä ja ehkäisykeinoja. Lisähuomiota kiinnitettiin bakteremian seurauksena kehittyneisiin tekonivelinfektioihin. Prospektiivisen infektioseurannan kautta tunnistettujen tekonivelinfektiotapausten lisäksi tekonivelinfektioiden tunnistamiseen käytettiin mikrobiologisia tuloksia, sairaalan hoitoilmoitusrekisteriä ja infektion vuoksi tehtyjä revisioleikkauksia. Tämä tehtiin, jotta tekonivelinfektiot saataisiin tunnistettua mahdollisimman kattavasti, erityisesti myöhäisten tekonivelinfektioiden osalta, koska näitä ei löydetä tavanomaisessa infektioseurannassa.

Tekonivelinfektion ilmaantuvuus oli 0,68% (158/23171) vuoden seurannassa ensitekonivelleikkauksen jälkeen. Lonkissa ilmaantuvuus oli hieman matalampi kuin polvissa: 0,57% vs. 0,77%. Pidemmässä seurannassa (12 vuoteen saakka)

tekonivelinfektion ilmaantuvuus oli 1,50% ja ilmaantumistiheys 3,3 tuhatta henkilövuotta kohti.

Niistä 405:stä tekonivelinfektiotapauksesta, jotka täyttivät joko toiset tai molemmat tekonivelinfektion määritelmät, 73 (18%) täyttivät ainoastaan vanhemmat kriteerit, kun taas pelkästään uudet kriteerit täyttäviä oli ainoastaan yksi (0,2%). Tekonivelinfektion diagnoosi perustui kliinikon mielipiteeseen 39:ssä (53%) niistä tapauksista, jotka eivät täyttäneet uutta tekonivelinfektion määritelmää.

Aiemmin raportoiduista tekonivelinfektion riskitekijöistä miessukupuoli (OR 2,21, 95% luottamusväli (LV) 1,56–3,11), polven tekonivel (OR 1,43, 95% LV 1,01–2,04) ja ikä (OR 1,03, 95% LV 1,01–1,05) lisäsivät tekonivelinfektion riskiä monimuuttujamallissa vuoden seurannassa. Diabeteksen vaikutus tekonivelinfektioriskiin oli lähes tilastollisesti merkittävä (OR 1,64, 95% LV 0,99–2,73).

Leikkausta edeltävä bakteriuria ei toisaalta lisännyt tekonivelinfektion riskiä yhden muuttujan (OR 0,72, 95% LV 0,34–1,54) tai monimuuttujamallissa (OR 0,82, 95% LV 0,38–1,77) vuoden seurannassa. Leikkausta edeltävässä virtsanäytteessä kasvaneiden taudinaiheuttajien ja tekonivelinfektion aiheuttajien välillä ei myöskään todettu yhteyttä, eikä bakteriurian hoitaminen tehokkailla antibiooteilla vähentänyt tekonivelinfektion riskiä (OR 0,62, 95% LV 0,07–5,14). Leikkausta edeltävä oraalisten antibioottien käyttö kuitenkin liittyi vähentyneeseen tekonivelinfektion riskiin (OR 0,40, 95% LV 0,22–0,73) ja antibioottien käyttö ylipäänsä ennen tekonivelleikkausta oli yleistä: 4106:tta (18%) tekonivelleikkausta edelsi yksi tai useampia antibioottikuureja.

Pidemmässä seurannassa (12 vuoteen saakka) 3,8% (542/14378) potilaista, joilla oli tekonivel, sairasti veriviljelypositiivisen infektion. Useampia bakteremioita oli 85:lla potilaalla, ja kaiken kaikkiaan bakteremiaepisodeja oli 643. Yleisin veriviljelypositiivisen infektion aiheuttaja oli *Escherichia coli* (241/643, 37%). Tekonivelinfektio bakteremian seurauksena kehittyi seitsemässä prosentissa (46/643) veriviljelypositiivisista infektioista. Riski oli suurin beetahemolyyttisille streptokokeille (21%, 12/58), *Staphylococcus aureukselle* (20%, 21/105) ja viridans-ryhmän streptokokeille (16%, 4/25) ja pienin gramnegatiivisille bakteereille (1,3%, 4/314). Koagulaasinegatiivisten stafylokokkien aiheuttamiin bakteremioihin ei myöskään liittynyt yhtään tekonivelinfektiota. Bakteremian seurauksena kehittyneen tekonivelinfektion riskiä lisäsivät toistuvat bakteremiat (OR 2,29, 95% LV 1,17–4,50) ja riski oli suurin vuoden sisään edeltävästä leikkauksesta ilmaantuneille bakteremioille. Pitkäaikaissairaudet tai muut potilaisiin liittyvät tekijät eivät kuitenkaan lisänneet tekonivelinfektioriskiä bakteremian aikana.

Yhteenvetona voidaan todeta, että eri tekonivelinfektion määritelmät eivät ole yhtenäisiä keskenään ja tämä tulisi huomioida tutkimustyössä ja seurannassa. Uusien, objektiivisempien kriteerien myötä tunnistettujen tekonivelinfektioiden määrä on pienempi. Toisaalta kliinikkojen tunnistamista tekonivelinfektioista suuri osa ei täyttänyt uusia tekonivelinfektion diagnostisia kriteerejä. Tekonivelinfektion määrittämiseen ei edelleenkään ole olemassa kultaista standardia, jota voitaisiin käyttää tutkimustyössä tai seurannassa.

Tutkimuksen tulosten perusteella leikkausta edeltävän virtsanäytteen tutkiminen oireettomilta potilailta ei ole hyödyllistä tekonivelinfektion ehkäisyssä, ei myöskään oireettoman bakteriurian hoitaminen antibiootein. Leikkausta edeltävän antibioottien käytön ja vähentyneen tekonivelinfektioriskin yhteyttä ei ole aikaisemmin tutkittu tai raportoitu, joten tämän löydöksen merkitys täytyy arvioida myöhemmissä tutkimuksissa. Bakteremian aiheuttamaan tekonivelinfektioriskiin vaikuttavia muokattavissa olevia potilaskohtaisia tekijöitä ei pystytty osoittamaan, mutta tekonivelinfektioriskin arvioinnissa veriviljelypositiivisen infektion yhteydessä täytyy ottaa huomioon taudinaiheuttaja, potilaan infektiohistoria ja infektion ajankohta edeltävään leikkaukseen nähden.

CONTENTS

ABBREVIATIONS

95% CI	Ninety-five percent confidence interval
ASA	American Society of Anesthesiologists
ASB	Asymptomatic bacteriuria
ATC	Anatomical Therapeutic Chemical Classification System
BMI	Body mass index
CDC	Centers for Disease Control and Prevention
CoNS	Coagulase-negative staphylococci
CRP	C-reactive protein
CT	Computed tomography
ESR	Erythrocyte sedimentation rate
FDG-PET/CT	^{18F}-fluorodeoxyglucose positron emission tomography with CT
HAI	Healthcare-associated infection
ICD-10	International Classification of Diseases, 10th edition
IDSA	Infectious Diseases Society of America
IL-6	Interleukin-6
LE	Leucocyte esterase
MRI	Magnetic resonance imaging
MRSA	Methicillin-resistant *Staphylococcus aureus*
MSIS	Musculoskeletal Infection Society
NGS	Next-generation sequencing
NNIS	National Nosocomial Infections Surveillance
NNT	Number needed to treat
OR	Odds ratio
PCR	Polymerase chain reaction
PJI	Periprosthetic joint infection
PMN	Polymorphonuclear neutrophil
SAB	*Staphylococcus aureus* bacteremia
SAI	Local healthcare-associated infection register of the Tampere University Hospital

SD	Standard deviation
SIRO	Finnish Hospital Infection Program
SPECT/CT	Single-photon emission computed tomography-CT
SSI	Surgical-site infection
UTI	Urinary tract infection
WBC	White blood cell

ORIGINAL PUBLICATIONS

This thesis is based on the following papers that are referred to in the text by their Roman numerals. Some additional data has been added as well.

I Honkanen M, Jämsen E, Karppelin M, Huttunen R, Lyytikäinen O, Syrjänen J. Concordance between the old and new diagnostic criteria for periprosthetic joint infection. Infection, 2017; 45: 637-43

II Honkanen M, Jämsen E, Karppelin M, Huttunen R, Huhtala H, Eskelinen A, Syrjänen J. The impact of preoperative bacteriuria on the risk of periprosthetic joint infection after primary knee or hip replacement: a retrospective study with a 1-year follow up. Clin Microbiol Infect, 2018; 24(4): 376-380

III Honkanen M, Jämsen E, Karppelin M, Huttunen R, Syrjänen J. The effect of preoperative oral antibiotic use on the risk of periprosthetic joint infection after primary knee or hip replacement: a retrospective study with a 1-year follow-up. Clin Microbiol Infect, 2019; 25(8):1021-1025

IV Honkanen M, Jämsen E, Karppelin M, Huttunen R, Eskelinen A, Syrjänen J. Periprosthetic joint infections as a consequence of bacteremia. Open Forum Infect Dis, 2019; 6(6)

1 INTRODUCTION

Joint replacement surgery is one of the most common and successful forms of orthopedic surgery performed, with over one million hip and knee replacements performed globally each year. Most of the joint replacements are placed in hip or knee joints. Over 90% of primary total joint replacement surgeries are performed due to primary osteoarthritis, other reasons include inflammatory arthritis, especially rheumatoid arthritis, and previous trauma. The number of joint replacement surgeries is continually increasing, as the population is ageing and osteoarthritis becomes more prevalent. (Ferguson et al., 2018; Price et al., 2018.) However, the number of joint replacements performed due to rheumatoid arthritis has decreased (Jämsen et al., 2013).

Periprosthetic joint infection (PJI) is a catastrophic, but rare, complication of joint replacement surgery, with significant morbidity and costs to the healthcare system as well as increased mortality (Gundtoft et al., 2017b). The occurrence of a PJI increases the costs related to joint replacement surgery and the length of stay in a hospital two- to four-fold when compared to noninfected joint replacements (Kapadia et al., 2014; Kapadia et al., 2016b; Klouche et al., 2010; Kurtz et al., 2008). The annual cost of treating PJIs in the United States has been projected to exceed 1.6 billion USD in 2020 (Kurtz et al., 2012). Besides the financial costs, a PJI also affects patients' quality of life negatively, especially physical functioning (Rietbergen et al., 2016), and the mortality risk more than doubles when compared with patients with joint replacements, but no need for revision surgery (Gundtoft et al., 2017b).

PJIs pose several difficulties to the healthcare system: they can be difficult to diagnose and they can occur at any time after joint replacement surgery. In addition, treatment of PJIs is complex and expensive, and it usually requires revision surgery. In fact, about one fourth of revision surgeries are performed because of an infection (Bohm et al., 2012; Bozic et al., 2010).

Treatment of PJIs is often time consuming. Treatment options depend on the timing of the onset of symptoms relative to the primary operation and the causative pathogen. In general, early and acute PJIs can be treated surgically with debridement and implant retention, whereas delayed and chronic infections require one- or two-

stage revision surgery. Rarely, arthrodesis or amputation is needed in difficult-to-treat cases. (Kapadia et al., 2016a; Osmon et al., 2013.) In addition to surgery, antibiotic treatment is needed. The overall duration of antibiotic treatment lasts from weeks to months, and occasionally lifelong suppressive antibiotic therapy is required (Osmon et al., 2013).

Due to the increased burden on the healthcare system and patients' lives caused by PJIs, it is extremely important to prevent them. Therefore, attempts have been made to identify risk factors for PJI and preventive measures are implemented at different stages of joint replacement surgery. The level of evidence for each measure is varied, however, and practices differ considerably on a national and international level. In order to form uniform policies regarding the diagnosis, prevention and treatment of PJIs, two international consensus meetings have been held in 2013 and 2018. Importantly, more objective diagnostic criteria for PJI were introduced in the meeting in 2013. (*Proceedings of the international consensus meeting on periprosthetic joint infection.* 2013; Parvizi et al., 2019). Important research questions identified in the first consensus meeting also include, among others, the role of urinary tract screening before elective joint replacement and the association between preoperative bacteriuria and subsequent PJI, preoperative skin decolonization and the role of prophylactic antibiotics.

The purpose of this study was to evaluate topics related to the diagnosis, risk factors and prevention of PJIs following primary hip or knee replacement. These include the concordance between the old and new diagnostic criteria for PJI, the effect of preoperative bacteriuria and preoperative oral antibiotic use on the risk for developing a subsequent PJI and finally, the risk for developing a PJI as a consequence of bacteremia. In addition, pathogens causing different types of PJIs were examined.

2 REVIEW OF THE LITERATURE

2.1 Healthcare-associated infections

In general, the term healthcare-associated infection (HAI) is used to separate infections related to procedures or to the use of invasive devices employed in the treatment of patients or acquired in a healthcare setting, from community-acquired infections. The CDC (Centers for Disease Control and Prevention) defines HAI as "a localized or systemic condition resulting from an adverse reaction to the presence of an infectious agent(s) or its toxin(s). There must be no evidence that the infection was present or incubating at the time of admission to the acute care setting". (Horan et al., 2008.) Furthermore, an infection is considered to be healthcare-associated only if it occurs on or after the 3rd calendar day after admission to an inpatient location (day of admission is calendar day 1) (Centers for Disease Control 2019).

HAIs can be caused by endogenous or exogenous infectious agents. Endogenous pathogens include microbes from the patient's own microbiome from body sites, such as the skin, upper respiratory tract, gastrointestinal tract or vagina. Exogenous sources are external to the patient, and include patient care personnel, visitors, patient care equipment, medical devices or the health care environment. (Horan et al., 2008.)

There are several infection prevention activities implemented against HAIs, as the burden they impose on the healthcare system is significant with increased morbidity and mortality, increased costs, and prolonged hospital stays. In a large survey from the United States, 4% of inpatients in acute care hospitals had at least one HAI (Magill et al., 2014).

2.1.1 Surgical-site infections and periprosthetic joint infections

Surgical-site infections (SSIs) are the most common form of HAIs along with pneumonia. Approximately one fifth of all HAIs are SSIs. (Magill et al., 2014.) According to the CDC definition, to be classified as having an SSI, the patient has to have undergone an operation where the surgeon has made at least one incision

through the skin or mucous membrane and closed the incision primarily before the patient has left the operating room (Horan et al., 1992).

SSIs have been divided according to the depth of infection into superficial and deep incisional SSIs and organ/space SSIs. A superficial infection involves only the skin or subcutaneous tissue of the incision, whereas a deep incisional infection involves deep soft tissues (i.e. fascial and muscle layers). An organ/space infection extends deeper and involves any part of the anatomy, excluding the incision, opened or manipulated during the operation. (Horan et al., 1992.) Organ/space SSIs can be further divided according to specific infection sites with specific criteria for each site. PJIs are always organ/space infections. Other examples include endocarditis, intracranial infection and urinary system infection. (Centers for Disease Control 2019.)

The differentiation between deep incisional SSI and PJI can be difficult due to anatomic reasons, especially in the case of knee replacements. In a validation study of the Finnish Hospital Infection Program (SIRO), Huotari et al. found that only half of the infections identified as PJIs by the validation team were classified as such by routine surveillance. Almost half were classified as deep incisional SSIs. (Huotari et al., 2007b.)

For an SSI to develop, a microbial contamination of the surgical site, either by endogenous or exogenous pathogens has to occur. Traditionally, it has been assumed that the risk for SSI is significantly increased if the surgical site is contaminated with $>10^5$ microorganisms per gram of tissue (Krizek & Robson, 1975). However, the number of contaminating microbes needed to produce an infection may be much lower if foreign material (such as a joint replacement) is introduced to the surgical site (Zimmerli et al., 1982).

During the development of a PJI, after microbial colonization of the joint replacement, the dividing microbes produce a biofilm. It is a polymeric matrix that protects the microbes from host defense responses and antimicrobial agents. Furthermore, the microbes in the biofilm may enter a stationary growth phase, making them more resistant to antimicrobials that affect cell division. (Zimmerli et al., 2004) Because of these factors, antimicrobial treatment on its own is usually not sufficient in the treatment of PJIs, and a removal of the infected joint replacement is usually needed.

2.2 Definition and diagnostics of periprosthetic joint infection

2.2.1 Diagnostic tests

There is not a single diagnostic test to identify a PJI, but many different methods have been used in clinical practice and studied, either alone or in combination with other tests. In clinical practice, a step-wise approach to diagnosing PJIs is recommended, starting with clinical examination and serologic markers before moving on to more invasive examinations (Abdel Karim et al., 2019; Della Valle et al., 2011).

The most common symptom that raises a suspicion of a PJI is persistent pain in the joint. Early infections can also present with induration or edema, a draining wound, surgical site erythema and effusion. (Kapadia et al., 2016a; Osmon et al., 2013; Zmistowski et al., 2014.) Pain is not a specific symptom for infection, however, but can be caused by other reasons as well. A more specific finding is a sinus tract from the skin to the joint, and it has been considered to be enough on its own for a diagnosis of a PJI (Zmistowski et al., 2014).

Once a suspicion of a PJI has been raised, a number of diagnostic tests can be applied, these are outlined below. Sensitivities and specificities of various diagnostic tests are given in Table 1. There is great variation in these, mainly because the cut-off values and reference standards vary considerably between studies.

Table 1. Sensitivities and specificities of various diagnostic tests in identifying a PJI (from previously published studies and review papers)

Diagnostic test	Sensitivity	Specificity
Serology *		
C-reactive protein (CRP)	0.86 – 0.96	0.20 – 0.92
Erythrocyte sedimentation rate (ESR)	0.75 – 0.97	0.33 – 0.89
CRP and ESR in combination	0.75 – 0.95	0.29 – 0.89
White blood cell count	0.20 – 0.70	0.60 – 0.96
Interleukin-6	0.87 – 0.95	0.87 – 0.90
Procalcitonin	0.33	0.98
Synovial fluid and tissue samples †		
Culture of synovial fluid	0.56 – 0.86	0.88 – 1.00
Culture of periprosthetic tissue	0.61 – 0.94	0.92 – 1.00
Culture of sonicate-fluid	0.73 – 0.97	0.90 – 1.00
Polymerase chain reaction testing of synovial fluid, periprosthetic tissue or sonicate-fluid	0.67 – 0.96	0.12 – 1.00
Synovial fluid white blood cell count	0.36 – 0.94	0.80 – 0.99
Synovial fluid polymorphonuclear neutrophil percentage	0.84 – 1.00	0.82 – 0.98
Histopathology of periprosthetic tissue	0.73 – 0.94	0.94 – 0.98
Synovial fluid leucocyte esterase	0.29 – 1.00	0.64 – 1.00
Synovial fluid α-defensin	0.63 – 1.00	0.95 – 1.00
Synovial fluid CRP	0.82 – 0.92	0.88 – 1.00
Next-generation sequencing of periprosthetic tissue or synovial fluid	0.89	0.73
Imaging techniques ‡		
Bone scintigraphy	0.68 – 1.00	0.15 – 0.90
Gallium scintigraphy	0.37 – 0.95	1.00
Leucocyte labeled scintigraphy	0.50 – 1.00	0.45 – 1.00
^{18F}-fluorodeoxyglucose positron emission tomography	0.64 – 1.00	0.67 – 0.97

*, (Berbari et al., 2010b; Bottner et al., 2007; Cipriano et al., 2012; Gallo et al., 2018; Ghanem et al., 2009; Johnson et al., 2011; Schinsky et al., 2008); †, (Atkins et al., 1998; Barrack & Harris, 1993; Cipriano et al., 2012; De Vecchi et al., 2016; Deirmengian et al., 2014; Dinneen et al., 2013; Gallo et al., 2018; Ghanem et al., 2008; Lee et al., 2017; Liu et al., 2017; Lonner et al., 1996; Melendez et al., 2014; Mitchell et al., 2017; Parvizi et al., 2011a; Portillo et al., 2012; Rothenberg et al., 2017; Schinsky et al., 2008; Spangehl et al., 1999; Tarabichi et al., 2018a; Trampuz et al., 2004; Trampuz et al., 2007; Yan et al., 2018); ‡, (Diaz-Ledezma et al., 2015; Palestro, 2014)

2.2.1.1 Serology

Traditional inflammatory markers, C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR), can be used as screening tools in the diagnosis of PJI and have been widely studied (Berbari et al., 2010b; Bottner et al., 2007; Cipriano et al., 2012; Ghanem et al., 2008; Johnson et al., 2011; Schinsky et al., 2008). Their use is also recommended by the international consensus statement from 2018 (Barrack et al., 2019). CRP and ESR have a poor specificity, but are usually elevated in cases of PJI (Table 1), even though there are reports of PJIs with normal CRP and ESR values (McArthur et al., 2015). ESR value higher than 30 millimeters per hour and CRP

value more than 10 milligrams per liter are generally used as cut-off values suggestive of a PJI, except in the immediate post-operative period (<6 weeks), when higher cut-off values are recommended (Zmistowski et al., 2014).

Novel serum inflammatory markers, such as interleukin-6 (IL-6) and procalcitonin, have also been studied with respect to PJIs (Barrack et al., 2019; Bottner et al., 2007). Especially IL-6 has shown a good sensitivity and specificity when compared to more traditional serology testing, but as the number of studies is still fairly small, it has not been adopted to routine use (Berbari et al., 2010b; Xie et al., 2017).

2.2.1.2 Synovial fluid and tissue samples

A microbial culture from the affected joint, either from a synovial fluid aspirate or from a tissue or synovial fluid sample taken intraoperatively, has been a traditional method to identify the presence or absence of infection (Bauer et al., 2006). There are problems associated with this, however. A positive bacterial culture can be the result of a contamination, especially in the case of skin commensals, such as coagulase-negative staphylococci (CoNS), corynebacteria or *Cutibacterium acnes* (Atkins et al., 1998; Barrack & Harris, 1993; Lonner et al., 1996). On the other hand, a PJI can be culture-negative, for example due to prior use of antibiotics (Berbari et al., 2007; Klement et al., 2018; Malekzadeh et al., 2010). In addition, the optimal number of samples that should be obtained for culture to accurately diagnose a PJI has been under debate. Earlier studies recommended obtaining five or six samples in order to gain optimal diagnostic accuracy (Atkins et al., 1998), but more recent studies have shown that four samples might be the optimal number (Bemer et al., 2016; Gandhi et al., 2017; Peel et al., 2016).

In order to improve the sensitivity of microbial cultures, different techniques have been applied. These include experimental techniques, such as extracting the pathogens from the tissue samples using a beadmill technique (Bemer et al., 2016; Roux et al., 2011) or, more commonly, using sonication to break the biofilm and dislodge pathogens from the surface of the prosthesis and culturing the resulting sonicate-fluid (Liu et al., 2017; Rothenberg et al., 2017; Trampuz et al., 2007).

The use of polymerase chain reaction (PCR) analysis, either from synovial fluid, tissue samples or sonicate-fluid, has been examined with varying results (Table 1) (Gallo et al., 2008; Jacovides et al., 2012; Melendez et al., 2014; Portillo et al., 2012). In general, it has been problematic to find a balance in the PCR technique between

optimal sensitivity and specificity without the other suffering too much (Mitchell et al., 2017).

In addition to culture samples and PCR, synovial fluid can be used for many other analyses. Among the most commonly used are the white blood cell (WBC) count and the polymorphonuclear neutrophil (PMN) percentage. There has been a problem in defining universally accepted cut-off values for these, however. Studies have proposed cut-off values with high sensitivity and specificity ranging from 1100/μl to 3450/μl for WBC count and from 64% to 78% for the PMN percentage (Cipriano et al., 2012; Dinneen et al., 2013; Ghanem et al., 2008; Trampuz et al., 2004). On the other hand, the international consensus meeting guidelines from 2013 suggest much higher cut-off values: WBC count >10 000 for early infections and >3 000 for delayed and late infections and PMN% >90% for early infections and >80% for delayed and late infections (Zmistowski et al., 2014).

There has been a wish to obtain results from the synovial fluid analysis faster, and to this end, the use of leucocyte esterase (LE) strip test has been proposed. LE is an enzyme secreted by neutrophils at the site of infection and has been commonly used in the diagnosis of urinary tract infections (Parvizi et al., 2011a). It can be used for point-of-care analysis of the synovial fluid, but again, when used alone to diagnose PJIs, it has shown varying sensitivity and specificity (Table 1).

Histopathological analysis of intraoperative tissue samples can also be indicative of a PJI, especially if a systematic analysis on the number of PMNs per high-power field is used, but this requires a pathologist experienced in interpreting periprosthetic tissue (Tsaras et al., 2012a).

2.2.1.3 Imaging techniques

Imaging techniques that can aid in the diagnosis of a PJI either do not require radio-isotopes [plain radiographs, ultrasonography, computed tomography (CT) scanning or magnetic resonance imaging (MRI)] or do require them (bone scintigraphy, gallium scintigraphy, leucocyte labeled scintigraphy or FDG-PET/CT) (Arvieux & Common, 2018; Palestro, 2014; Palestro & Love, 2017). None of these methods have a fixed role in the diagnostic process of a PJI, however, and they have not been included in the diagnostic criteria proposed by the international consensus meeting in 2013 (Zmistowski et al., 2014).

Patients with a PJI often have normal plain radiographs and thus they are not very useful in diagnosing a PJI (Tigges et al., 1994). They are still recommended as a first-line imaging modality when suspecting a PJI and are routinely used, especially

because they can be used to identify other reasons for joint failure (Kapadia et al., 2016a; Osmon et al., 2013). CT scans or MRI can provide additional information, and they can show signs suggestive of a PJI, such as joint effusion, local edema, bone destruction and reactive lymphadenopathy, but these are usually not enough to confirm the diagnosis, as they are non-specific findings (Fritz et al., 2014).

In recent years, several radionuclide imaging techniques have been applied to the diagnosis of PJIs. Older techniques, such as bone scintigraphy with technetium-99m labeled diphosphonate and gallium scintigraphy, have been mostly replaced by newer ones (Palestro, 2014). These include leucocyte labeled scintigraphy with or without a bone scan or bone marrow imaging and FDG-PET, often combined with a CT scan. These have both shown similar sensitivities and specificities (Table 1). However, there has been a debate as to which one of these methods should be the imaging technique of choice when diagnosing a PJI (Kwee et al., 2017; Palestro, 2014). Furthermore, there has been a concern that the radionuclide imaging techniques might not offer any additional benefit in the diagnosis of a PJI when compared to other diagnostic modalities, and should therefore be reserved only to a selected group patients with difficult to diagnose infections (Diaz-Ledezma et al., 2015; Osmon et al., 2013).

2.2.1.4 Future possibilities

As PCR techniques have not shown great advantages over traditional culture in diagnosing PJI (Melendez et al., 2014; Mitchell et al., 2017), studies have recently focused on next-generation sequencing (NGS) and other molecular technologies as a an aid to diagnose PJIs and to identify pathogens causing them (Tarabichi et al., 2018a; Tarabichi et al., 2018b; Thoendel et al., 2018). These methods have shown high sensitivity, but specificity has not been optimal and a high number of false positive cases have been reported (Tarabichi et al., 2018a; Thoendel et al., 2018). Even though molecular technologies have shown promise in identifying pathogens in culture-negative PJIs, the cost and slow processing time limit these methods from being adopted to routine use at the moment (Thoendel et al., 2018).

There has also been great interest in different synovial fluid markers in the diagnosis of PJI, some being more promising than others (Deirmengian et al., 2014; Lee et al., 2017; Mitchell et al., 2017). A wide range has been studied (e.g. CRP, IL-6 and α-defensin), and some studies have even shown 100% sensitivity and specificity to markers such as α-defensin (Deirmengian et al., 2014). Nevertheless, none of these markers have shown superiority over others and none of them can be

used as a single test to diagnose a PJI. Furthermore, they cannot be used to identify the causing pathogen.

In the field of radionuclide imaging, there has been interest towards the development of infection-specific tracers, such as antimicrobial peptides, and the use of other imaging techniques, such as single-photon emission computed tomography-CT (SPECT/CT) (Palestro, 2014). Their role in the diagnosis of PJI remains to be determined.

2.2.2 Diagnostic criteria

A universal definition or diagnostic criteria for PJI are lacking. Different diagnostic criteria have been used in clinical practice, clinical studies and surveillance programs (Parvizi et al., 2011b). Most of these criteria are based on different combinations of microbiological cultures, histology, laboratory parameters and the intraoperative appearance of the affected joint (Parvizi et al., 2006; Parvizi et al., 2008; Schinsky et al., 2008; Spangehl et al., 1999; Trampuz et al., 2007). In SSI surveillance programs, PJIs have been defined according to the CDC criteria from the year 1992 (Horan et al., 1992). These include a diagnosis of infection by the treating clinician as one of the diagnostic criteria (Table 2).

Due to the lack of consensus on the definition of PJI, a new, more objective, set of criteria was proposed in 2011 by the Musculoskeletal Infection Society (MSIS) (Parvizi et al., 2011c). These were further modified in the international consensus meeting in 2013, where a new set of criteria was introduced. These two sets of criteria are compared with the old CDC criteria from 1992 in Table 2. The most notable difference between the old criteria and new ones is the removal of the clinician's diagnosis from the criteria set and the addition of specific laboratory tests in the minor criteria. The criteria from 2013 have also been adopted by the CDC (Centers for Disease Control 2019).

Table 2. Different diagnostic criteria for periprosthetic joint infection (Horan et al., 1992; Parvizi et al., 2011c; Zmistowski et al., 2014)

Centers for Disease Control criteria from 1992	Musculoskeletal Infection Society criteria from 2011	Consensus meeting criteria from 2013
Infection involves any part of the anatomy (e.g., organs or spaces), other than the incision, which was opened or manipulated during an operation	There is a sinus tract communicating with the prosthesis	A sinus tract communicating with the joint
	OR A pathogen is isolated by culture from at least two separate tissue or fluid samples obtained from the affected prosthetic joint	OR Two positive periprosthetic cultures with phenotypically identical organisms
AND Patient has at least one of the following:	OR Four of the following six criteria exist:	OR Having three of the following minor criteria:
Purulent drainage from a drain that is placed through a stab wound into the organ/space	Elevated serum erythrocyte sedimentation rate and C-reactive protein concentration	Elevated serum C-reactive protein and erythrocyte sedimentation rate *
Organisms isolated from an aseptically obtained culture of fluid or tissue in the organ/space	Elevated synovial leukocyte count	Elevated synovial fluid white blood cell count or change on leukocyte esterase test strip †
An abscess or other evidence of infection involving the organ/space that is found on direct examination, during reoperation, or by histopathologic or radiologic examination	Elevated synovial neutrophil percentage	Elevated synovial fluid polymorphonuclear cell percentage ‡
Diagnosis of an organ/space surgical site infection by a surgeon or attending physician	Isolation of a microorganism in one culture of periprosthetic tissue or fluid	A single positive culture
	Greater than five neutrophils per high-power field in five high-power fields observed from histologic analysis of periprosthetic tissue at x 400 magnification	Positive histological analysis of periprosthetic tissue
	Presence of purulence in the affected joint	

*, Cut-off values for CRP >100 for early infections (less than 6 weeks from previous operation) and >10 for delayed/late infections (over 6 weeks from previous operation), cut-off value for ESR >30 (delayed/late infections, ESR does not apply for early infections); †, Cut-off value for synovial fluid WBC count >10 000 for early infections and >3 000 for delayed/late infections; ‡, Cut-off value for PMN% >90% for early infections and >80% for delayed/late infections

In the 2011 MSIS criteria, the presence of purulence in the affected joint is one of the minor criteria in defining a PJI (Parvizi et al., 2011c). The Infectious Diseases Society of America (IDSA) guideline on PJI also states that purulence without any other apparent reason is definitive proof of a PJI (Osmon et al., 2013). Interestingly, this criterion was removed from the 2013 definition of PJI, as purulence has also

been found in cases of adverse local tissue reaction to metal-on-metal hip implants and determining its presence is subjective (Zmistowski et al., 2014).

In an attempt to formulate a validated set of diagnostic criteria for PJI, Parvizi et al. developed yet another set of criteria in 2018, as the previous criteria were based on expert opinion and not validated (Parvizi et al., 2018). These criteria were further revised and presented in the international consensus meeting in 2018 (Shohat et al., 2019). This set of criteria is more complex than the previous ones, and different diagnostic tests have different weights (Table 3). It also incorporates novel diagnostic tests for PJI, such as serum D-dimer and synovial fluid α-defensin. Interestingly, purulence in the affected joint is one of the minor criteria for infection, as it was removed from the previous consensus meeting criteria set. However, these criteria reached only a weak consensus in the consensus meeting in 2018 and have not been endorsed by larger organizations, so their role in the diagnosis of PJI remains to be established.

Table 3. The diagnostic criteria for PJI proposed in 2018 (Parvizi et al., 2018; Shohat et al., 2019)

Major criteria (at least one of the following)				**Decision**
Two positive cultures of the same organism				Infected
Sinus tract with evidence of communication to the joint or visualization of the prosthesis				
Minor criteria	**Threshold**		**Score**	
	Acute*	**Chronic**		Combined minor
Elevated serum C-reactive protein (mg/l)	100	10	2	criteria score:
or				≥ 6 Infected
D-Dimer (μg/l)	Unknown	860		3–5 Inconclusive†
				<3 Not infected
Elevated erythrocyte sedimentation rate (mm/hour)	No role	30	1	
Elevated synovial white blood cell count (/μl)	10 000	3 000	3	
or				
leukocyte esterase	++	++		
or				
positive α-defensin (signal/cutoff)	1.0	1.0		
Elevated synovial polymorphonuclear cell percentage	90	70	2	
Single positive culture	-	-	2	
Positive histology	-	-	3	
Positive purulence‡	-	-	3	

*, Criteria not validated for acute infections; †, Consider further molecular diagnostics such as next-generation sequencing; ‡ Not applicable in suspected adverse local tissue reaction

2.3 Surveillance and epidemiology of periprosthetic joint infections

2.3.1 Surveillance programs

Due to the considerable morbidity and costs, SSIs following joint replacement surgery, especially PJIs, are part of most SSI surveillance programs (Grammatico-Guillon et al., 2015b). In Finland, surveillance data is gathered by hospitals participating in the Finnish Hospital Infection Program (SIRO) of the National Institute of Health and Welfare. The program was established in 1999 and orthopedic operations were among the first surgical procedures under surveillance. (Huotari et al., 2007b.) In validation studies of the SIRO program, sensitivities of 36–75% and a specificity of 100% have been reported for orthopedic SSIs (Huotari et al., 2010; Huotari et al., 2007b). Currently, of the 14 hospitals participating in the surveillance program, 12 hospitals report SSIs following hip replacement surgery and 11 hospitals following knee replacement surgery (Leikkausalueen sairaalainfektiot - julkinen raporttitiiviste).

The SSI surveillance programs are based on active and prospective infection surveillance. In order to gather reliable and comparable data, uniform definitions for SSIs should be used. Most surveillance programs are based on the National Nosocomial Infections Surveillance (NNIS) methodology and CDC definitions from the 1990s (Horan et al., 1992), but there are considerable differences nationally and internationally in the length of follow-up, the use of post-discharge surveillance, how the data is collected and reported and how feedback is given to the participating hospitals (Grammatico-Guillon et al., 2015b). The use of post-discharge surveillance, or the lack of it, is especially problematic in terms of comparing data from different centers and countries, as it can affect the incidence numbers greatly (Huotari et al., 2006).

Organized infection surveillance is important, as it has been shown to reduce the incidence of SSIs and to be cost-effective (Gastmeier et al., 2002; Haley et al., 1985; Wilson et al., 2006). Furthermore, reliable surveillance data can be used to assess quality of care, and it can also be used in benchmarking.

2.3.2 Epidemiology

The number of primary hip and knee replacements is continually rising, both globally (Ferguson et al., 2018; Price et al., 2018) and nationally in Finland (Järvelin et al., 2018). In 2018, there were 9 632 primary hip replacements and 12 092 primary knee replacements in Finland, and the number of primary joint replacement surgeries has more than doubled when compared to the year 2000. However, the number of revision joint replacements has not increased in the recent years. There were 1 537 revision hip replacements and 913 revision knee replacements in Finland in 2018. (Kovanen et al., 2019.)

The occurrence of a PJI after joint replacement surgery is fairly rare, occurring in approximately 1% of the cases. The incidences of PJI after primary hip and knee replacements in recent studies are presented in Tables 4 and 5. Overall, the incidence of PJI is higher for knee replacements than for hip replacements. The variation between studies in incidence numbers for PJI is mostly due to differences in follow-up times and definition of infection. Slightly different rates have also been found in single-center and national register-based studies, as national registers have a tendency to underestimate the incidence of infection (Jämsen et al., 2009b).

The incidence of PJI is higher after revision joint arthroplasty than after primary joint replacement (Kurtz et al., 2008; Poss et al., 1984). PJI rates up to 8% for hips and 15% for knees have been described for revision joint replacement (Kurtz et al., 2008) and the risk for PJI is more than doubled after revision joint replacement surgery when compared with primary joint replacements (Kunutsor et al., 2016).

Even though the incidence of PJI has decreased from the early years of joint replacement surgery due to the adoption of effective preventive measures (Schmalzried et al., 1992), there have been conflicting reports on the incidence numbers during recent years. Some studies have reported an increasing incidence for PJI after primary joint replacement surgery (Dale et al., 2012; Grammatico-Guillon et al., 2015a), while others have reported stable (Gundtoft et al., 2017a; Phillips et al., 2006) or decreasing incidences (Wang et al., 2018). In a large study, Kurtz et al. reported a significant rise in the incidence of PJI during 1990–2004, but this was only for revision surgeries. The incidence of PJI after primary joint replacements actually decreased during the study period. (Kurtz et al., 2008.) Nevertheless, the number of very late PJIs, occurring after five years from primary surgery, seems to be increasing (Huotari et al., 2015). This is probably due to the fact that the number of replaced joints is increasing and thus also the number of joints at risk for developing a PJI is increasing.

Table 4. The incidence of periprosthetic joint infection (PJI) for primary hip replacements in different studies*

Study	Number of operations	Methodology	Follow-up time (years)	Definition of infection	Incidence (%)
Blom et al. 2003	1 567	Postal questionnaires to patients and patient chart review retrospectively	5 –8	NA	0.45
Phillips et al. 2006	5 947	Prospective surveillance	Up to 15	Culture/radiology/clinical features	0.57
Huotari et al. 2007	5 614	National register-based study	1	CDC (also deep incisional included)	0.4
Pulido et al. 2008	5 060	Retrospective review of prospectively collected data	1–6	Serology/clinical features/radiology/culture/purulence	0.3
Ong et al. 2009	39 929	National register-based study	Up to 10	Diagnosis code	2.2
Huotari et al. 2010	7 561	National register-based study	1	CDC	1.6
Dale et al. 2011	5 540	National register-based study	1	CDC (also deep incisional included)	1.3
Dale et al. 2012	432 168	Nordic arthroplasty register-based study	Up to 16	Revision surgery due to infection	0.6
Huotari et al. 2015	50 272	National register-based study	1–13	Revision surgery due to infection or diagnosis code	0.92
Grammattico-Guillon et al. 2015	21 633	Retrospective cohort study	1–4	Revision surgery due to infection or diagnosis code	1.8
Gundtoft et al. 2015	32 896	National register-based study	1–7	Revision surgery due to infection or diagnosis code	1.0
Gundtoft et al. 2017	48 867	National register-based study	1	Revision surgery due to infection	0.6
Lenguerrand et al. 2018	623 253	National register-based study	Median 4.6	Revision surgery due to infection	0.43

*, (Blom et al., 2003; Dale et al., 2011; Dale et al., 2012; Grammatico-Guillon et al., 2015a; Gundtoft et al., 2015; Gundtoft et al., 2017a; Huotari et al., 2010; Huotari et al., 2015; Huotari et al., 2007a; Lenguerrand et al., 2018; Ong et al., 2009; Phillips et al., 2006; Pulido et al., 2008)

Table 5. The incidence of periprosthetic joint infection (PJI) for primary knee replacements in different studies*

Study	Number of operations	Methodology	Follow-up time (years)	Definition of infection	Incidence (%)
Blom et al. 2004	931	Postal questionnaires to patients and patient chart review retrospectively	5–8	NA	1.0
Phillips et al. 2006	4 788	Prospective surveillance	Up to 15	Culture/radiology/clinical features	0.86
Huotari et al. 2007	4 217	National register-based study	1	CDC (also deep incisional included)	0.9
Pulido et al. 2008	4 185	Retrospective review of prospectively collected data	1–6	Serology/clinical features/radiology/culture/purulence	1.1
Jämsen et al. 2009	35 421	National register-based study	1	Revision surgery due to infection	0.52
Kurtz et al. 2010	69 663	National register-based study	Up to 10	Diagnosis code	2.0
Huotari et al. 2010	5 921	National register-based study	1	CDC	1.3
Jämsen et al. 2010	2 647	Retrospective review of prospectively collected data	1	Modified CDC	0.8
Huotari et al. 2015	62 436	National register-based study	1–13	Revision surgery due to infection or diagnosis code	1.41
Grammattico-Guillon et al. 2015	11 045	Retrospective cohort study	1–4	Revision surgery due to infection or diagnosis code	2.0
Tayton et al. 2016	64 566	National register-based study	1	Revision surgery due to infection	0.28
Wang et al. 2018	10 768	Retrospective cohort study	Up to 15	Revision surgery due to infection	1.65
Lenguerrand et al. 2019	679 010	National register-based study	Median 4.6	Revision surgery due to infection	0.54

*. (Blom et al., 2004; Huotari et al., 2010; Huotari et al., 2007a; Jämsen et al., 2010b; Jämsen et al., 2009b; Kurtz et al., 2010; Lenguerrand et al., 2019; Phillips et al., 2006; Pulido et al., 2008; Tayton et al., 2016; Wang et al., 2018)

Most of the PJIs appear during the first postoperative year, with the incidence rate falling during the second and third year and then remaining stable or slightly decreasing over the years (Huotari et al., 2015; Kurtz et al., 2010; Ong et al., 2009; Tsaras et al., 2012b). It has been estimated that 25–47% of the PJIs after primary hip or knee replacement occur during the first three postoperative months, 17–23% during 3–12 months after surgery and 29–52% after one year (Grammatico-Guillon et al., 2015a; Huotari et al., 2015; Phillips et al., 2006; Pulido et al., 2008; Triffault-Fillit et al., 2018; Wang et al., 2018). However, when comparing these numbers, it should be taken into account that the proportion of late PJIs increases with longer follow-up times.

2.4 Types and microbiology of periprosthetic joint infections

PJIs have traditionally been classified as early (occurring within 3 months from prosthetic joint replacement surgery), delayed (occurring within 3–12 months) or late hematogenous infections (occurring after one year) (Coventry, 1975; Kapadia et al., 2016a). However, this division is somewhat arbitrary, as for example hematogenous infections can occur at any time after joint replacement surgery (Rodriguez et al., 2010; Stefánsdóttir et al., 2009).

Early and delayed infections are caused by direct contamination of the prosthesis during surgery or soon after it. Early infections present with an acute onset of symptoms, whereas delayed infections have a longer period of symptom development. Traditionally, early infections are postulated to be caused by virulent pathogens such as *S.aureus* or gram-negative bacteria, and delayed infections by more non-virulent pathogens such as CoNS that take time to proliferate sufficiently to cause symptoms. (Kapadia et al., 2016a; Zimmerli et al., 2004.) However, in a study by Stefánsdóttir et al., CoNS were the most common pathogen in both early and delayed PJIs (Stefánsdóttir et al., 2009), whereas in another study by Pulido et. al, *S.aureus* was most commonly found in early and delayed PJIs (Pulido et al., 2008).

The source of hematogenous PJIs can be from the skin and soft tissues, urinary tract, dental sources (Maderazo et al., 1988; Zeller et al., 2018), cardiovascular system (Rakow et al., 2019), lungs (Cook et al., 2007) or the gastrointestinal tract (Uçkay et al., 2009). They are most often caused by *S.aureus*, followed by streptococci and

gram-negative bacteria (Rodriguez et al., 2010; Stefánsdóttir et al., 2009; Swan et al., 2011; Triffault-Fillit et al., 2018; Zeller et al., 2018).

The proportion of culture-negative PJIs has varied from 1% to 12% in different studies (Berbari et al., 1998; Peel et al., 2012; Tsaras et al., 2012b; Zeller et al., 2018). This variation is partly explained by the different number of samples from individual study patients used in different studies.

2.5 Risk factors for periprosthetic joint infection

Over the years, several studies have examined possible risk factors for PJI with varying results, with some factors associated with an increased risk for infection consistently and some with conflicting results across studies (Kunutsor et al., 2016; Zhu et al., 2015). Overall, the risk factors can be divided into patient-related preoperative factors, operation-related perioperative factors and patient- and joint-related postoperative factors. Patient-wise, the overall risk for PJI is a combination of several factors, and therefore the risk scores used for assessing the individual's risk for infection, such as the NNIS System surgical patient risk index score, are a combination of different types of factors (Berbari et al., 1998).

It is possible that risk factors for PJI, especially those related to postoperative wound healing, differ between hip and knee replacements, as has been suggested by Peel et al. (Peel et al., 2011). This can be mostly explained by the anatomical differences between the sites.

2.5.1 Preoperative factors

2.5.1.1 Chronic comorbidities

Several chronic comorbidities have been shown to increase the risk for developing a PJI, and the risk is especially high for patients with multiple comorbidities (Kurtz et al., 2010; Ong et al., 2009). The American Society of Anesthesiologists (ASA) score is a measure of the patients' overall condition, and higher ASA scores (i.e. patients with more comorbidities) have been associated with an increased risk for developing a PJI (Huotari et al., 2007a; Jämsen et al., 2010b; Lenguerrand et al., 2018; Lenguerrand et al., 2019; Pulido et al., 2008).

Rheumatic disease, especially as an indication for joint replacement surgery, has been shown to increase the risk for PJI (Bozic et al., 2012b; Jämsen et al., 2009a; Lenguerrand et al., 2018). The effect of other comorbidities has been varied in different studies. For example, in a large, but older study by Berbari et al., systemic malignancy was the only chronic comorbidity independently associated with an increased risk for PJI (Berbari et al., 1998), whereas in a more recent study by Grammatico-Guillon et al., liver disease was the only independent risk factor for PJI among comorbidities (Grammatico-Guillon et al., 2015a). On the other hand, Bozic et al. evaluated the effect of 29 different comorbidities and patient-related risk factors for PJI, and found that besides rheumatic disease, coagulopathy and preoperative anemia were independently associated with an increased risk for PJI for hip replacements (Bozic et al., 2012b) and congestive heart failure, chronic pulmonary disease, preoperative anemia, diabetes, depression, renal disease, pulmonary circulation disorders, obesity, psychoses, metastatic tumor, peripheral vascular disease, and valvular disease for knee replacements (Bozic et al., 2012a). Finally, in a very large cohort study consisting of 623 253 primary hip replacements, Lenguerrand et al. showed that chronic pulmonary disease, diabetes, liver disease and congestive heart failure increased the risk for PJI (Lenguerrand et al., 2018), with similar results reported for knee replacements in another large cohort study (Lenguerrand et al., 2019).

The effect of diabetes on the risk for PJI has been divergent between studies, even though two large meta-analyses have demonstrated a significant association between diabetes and the risk for PJI (Kunutsor et al., 2016; Zhu et al., 2015). Jämsen et al. also showed diabetes to be an independent risk factor for PJI, even when potential confounding factors, such as obesity, were taken into account (Jämsen et al., 2012) On the other hand, in a study by Kremers et al., the effect of diabetes on the risk for PJI was nonsignificant in a multivariable analysis that included, among other variables, also body mass index (BMI) (Kremers et al., 2015). Nevertheless, hyperglycemia has been shown to be an independent risk factor for PJI (Jämsen et al., 2010a), thus suggesting that it is likely that poorly controlled diabetes increases the risk for PJI whereas well-controlled diabetes may not have such a significant effect. This is also reflected in the most recent international consensus statement, where severely uncontrolled diabetes is suggested to be a contraindication for joint replacement surgery (Cizmic et al., 2019).

Obesity has been shown to be a significant risk factor for PJI in many studies (Bozic et al., 2012b; Grammatico-Guillon et al., 2015a; Jämsen et al., 2010b; Lenguerrand et al., 2018; Lübbeke et al., 2016; Pulido et al., 2008), even though not

all studies have found this association (Berbari et al., 1998). However, the definition of obesity differs between studies, thus making direct comparisons difficult. Others have used different cut-offs for BMI, such as 30 (Lenguerrand et al., 2018) or 40 (Pulido et al., 2008), while others have used it as a continuous variable (Jämsen et al., 2010b). In a prospective cohort study, Lübbeke et al. discovered that BMI ≥35 seemed to be a cut-off for the increased risk for PJI (Lübbeke et al., 2016). On the other hand, also undernutrition may increase the risk for infection (Grammatico-Guillon et al., 2015a).

2.5.1.2 Preoperative acute infections

It is generally accepted that active local cutaneous, subcutaneous or deep tissue infection at the joint replacement site preoperatively is a risk factor for subsequent PJI (Aggarwal et al., 2014; Cizmic et al., 2019), usually resulting in postponement of the surgery. Furthermore, dermatophyte infections of the feet might predispose the patient to a PJI postoperatively (Kimyai-Asadi et al., 1999), and they are usually screened and treated preoperatively, even though there is no data to support this practice.

Patients with an elective joint replacement have traditionally been screened preoperatively for bacteriuria (David & Vrahas, 2000; Rajamanickam et al., 2007), even though this practice has been questioned (Lamb et al., 2016; Mayne et al., 2016). Thus, the association between preoperative asymptomatic bacteriuria (ASB) and subsequent PJI is not clear. The prevalence of ASB in patients undergoing elective joint replacement surgery has varied between 3.2% and 36% (Bouvet et al., 2014; Cordero-Ampuero et al., 2013; Glynn & Sheehan, 1984; Martinez-Velez et al., 2016; Sousa et al., 2014; Weale et al., 2019). On the other hand, ASB is common in the overall population, especially in older women (Nicolle et al., 2005; Rodhe et al., 2008) and its treatment is not recommended in the general population (Nicolle et al., 2005).

Earlier retrospective studies have not shown an association between preoperative bacteriuria and PJI (Berbari et al., 1998; Glynn & Sheehan, 1984; Koulouvaris et al., 2009; Ritter & Fechtman, 1987), but only during the last decade have there been prospective studies on the subject. An increased risk for postoperative infection complications in patients with preoperative ASB has been reported in some studies (Ollivere et al., 2009; Sousa et al., 2014; Weale et al., 2019), but direct seeding to the replaced joint has not been shown.

2.5.1.3 Other patient-related factors

Even though usually the majority of patients undergoing joint replacement surgery are female, male gender has been shown in several studies to increase the risk for PJI (Grammatico-Guillon et al., 2015a; Jämsen et al., 2010b; Jämsen et al., 2009a; Kurtz et al., 2010; Lenguerrand et al., 2018; Ong et al., 2009; Tayton et al., 2016). Older age has also been proposed to be an independent risk factor for PJI, but in fact, in many studies its effect has not been statistically significant (Grammatico-Guillon et al., 2015a; Jämsen et al., 2010b; Jämsen et al., 2009a; Kurtz et al., 2010; Lenguerrand et al., 2018; Ong et al., 2009). In addition, smoking has been shown to increase the risk for PJI, probably due to the many unfavorable cardiovascular effects of smoking that can lead to poor wound healing and other complications (Cizmic et al., 2019).

Previous surgery of the joint that is to be replaced is also a risk factor for PJI (Kunutsor et al., 2016), even though arthroscopic surgery has not been associated with an increased risk (Aalirezaie et al., 2019b). In addition, revision joint replacement surgery has also been shown to be an independent risk factor of PJI (Kunutsor et al., 2016). Possibly the reasons for this are the increased scar tissue and dead space in the joint caused by previous surgery.

In a retrospective study to develop a risk score for identifying patients at risk for developing a PJI, Everhart et al. found that a history of staphylococcal septicemia was an independent risk factor for PJI (Everhart et al., 2016). The mechanism for this lasting effect could not be identified by the researchers, however, nor was it known whether the subsequent PJIs of the patients with staphylococcal septicemias were caused by staphylococci or other bacteria. Perhaps this result reflects the patients' susceptibility to infection in general, as lower extremity osteomyelitis or septic arthritis were also independent risk factors for PJI in the same study (Everhart et al., 2016).

Staphylococcal nasal and skin carriage are common among patients undergoing elective joint replacement surgery. Stefánsdóttir et al. showed that in preoperative samples taken from patients coming for primary joint replacement, 95% had CoNS in the groin and 77% in the nose (Stefánsdóttir et al., 2013). In addition, studies have found *S.aureus* colonization rates of 27–28% for the nares and 7% for the inguinal area among patients planned for joint replacement surgery (Kalmeijer et al., 2000; Stefansdottir et al., 2013). Furthermore, *S.aureus* carriage has been shown to be an independent risk factor for developing an SSI, and the only independent risk factor for SSIs caused by *S.aureus* (Kalmeijer et al., 2000).

2.5.2 Perioperative factors

The impact of several operation-related factors on the risk for PJI have been examined. The duration of surgery has been shown to have an effect on the risk for PJI (Anis et al., 2018; Huotari et al., 2007a; Jämsen et al., 2010b; Kurtz et al., 2010). The reason for this could be that more difficult anatomic and operative conditions might predispose to longer operative times and thus also to postoperative complications. There might also be longer wound exposure to airborne bacteria in longer operations. In addition, obesity is associated with longer operative times and this might explain part of the increased risk as well (Liabaud et al., 2013).

In their large study, Lenguerrand et al. showed that surgical techniques have an impact on the risk for PJI, whereas different forms of anesthesia do not (Lenguerrand et al., 2018). The experience of the surgeon does not seem to have an effect on the risk for PJI (Berbari et al., 1998; Lenguerrand et al., 2018).

The need for allogenic blood transfusion has been shown to increase the risk for PJI (Pulido et al., 2008). This is possibly caused by the immunomodulatory effects of the transfusion.

2.5.3 Postoperative factors

2.5.3.1 Wound infection

The development of a superficial SSI postoperatively is a major risk factor for developing a PJI afterwards (Berbari et al., 1998; Peel et al., 2011). Berbari et al. showed that other factors related to poor wound healing (e.g. wound drainage, hematoma and dehiscence) were also associated with an increased risk for PJI in a univariate analysis. However, their effect was not significant in a multivariable analysis. (Berbari et al., 1998) On the other hand, in a study by Peel et al., wound discharge was an independent risk factor for PJI (Peel et al., 2011).

2.5.3.2 Other immediate postoperative complications

Postoperative complications following joint replacement surgery, such as atrial fibrillation and acute myocardial infarction, may also increase the risk for developing a PJI (Pulido et al., 2008). It is possible that this is due to the comorbidities

predisposing patients to these complications or due to the need for aggressive anticoagulation involved in these conditions.

2.5.3.3 Other infections and hematogenous spread

After joint replacement, the patient is at a permanent risk of developing a hematogenous PJI from other infectious sources. It has been shown that 25–40% of patients with *S.aureus*-bacteremia (SAB) and a joint replacement develop a hematogenous PJI (Lalani et al., 2008; Makki et al., 2017; Murdoch et al., 2001; Sendi et al., 2011; Tande et al., 2016). The risk for developing a PJI as a consequence of bacteremia caused by other pathogens is unclear, because most reports on PJIs during bacteremia have been case studies (Chodos & Johnson, 2009; Law et al., 2017; Pepke, Lehner et al., 2013; Reboli et al., 1989). In their study, Uçkay et al. reported a PJI rate of 6% (5/81) in patients with any bacteremia, but the small number of infections precludes making any conclusions on the risk for PJI for different pathogens (Uçkay et al., 2009).

Hematogenous seeding from a remote infection to the joint replacement has been reported for various types of infection: skin and soft tissue infections, dental infections (Maderazo et al., 1988; Rakow et al., 2019; Zeller et al., 2018), urinary tract infections (UTIs) (Cordero-Ampuero & de Dios, 2010; Pepke et al., 2013; Poss et al., 1984; Wymenga et al., 1992), gastrointestinal infections (Rakow et al., 2019; Uçkay et al., 2009; Zeller et al., 2018), cardiovascular infections (Rakow et al., 2019) and respiratory tract infections (Cook et al., 2007). The most common source for hematogenous PJIs has varied between studies.

There are two studies that have assessed the rate of remote infections in patients with joint replacements and the subsequent risk for developing a PJI, both with a mean follow-up period of about six years. The rate of remote infections in these studies is shown in Table 6. In the study by Ainscow et al., recurrent skin infections were a risk factor for PJI, with 7.5% (3/40) of patients with skin infections developing a PJI (Ainscow & Denham, 1984). On the other hand, in the study by Uçkay et al., the incidence of PJI for skin infections was 2.7% (1/37), whereas it was 7.5% (4/53) for infections from the gastrointestinal tract (Uçkay et al., 2009). None of the patients in either study with UTIs or respiratory tract infections developed a PJI.

Table 6. The incidence of remote infections in patients with a joint replacement

Study	Number of patients	Urinary tract infection		Respiratory tract infection		Skin infection		Gastroinfestinal infection		Other	
	n	n	%	n	%	n	%	n	%	n	%
Ainscow et al. 1984	1 000	109	11	120	12	40	4	NA	NA	68	7
Uçkay et al. 2009	5 122	271	5	128	2	37	0.7	53	1	41	0.8

Risk factors, other than the type of primary infection, for developing a hematogenous PJI are not clear and have not been studied extensively. Tande et al. showed that the presence of three or more joint replacements increased the risk for PJI during SAB (Tande et al., 2016), but other patient-related risk factors for developing a PJI during bacteremia have not been found. In one study with a fairly small sample size, patients' age, gender, diabetes and rheumatic disease did not affect the risk for developing a PJI during SAB (Sendi et al., 2011). There are no studies on risk factors for developing a PJI during any bacteremia.

Patients who develop cellulitis with a joint replacement *in situ*, are at risk for developing a PJI due to contiguous spread of the infection to the prosthesis. The risk is especially high if the joint replacement is recent and if the infection is located near the replaced joint. (Wouthuyzen-Bakker et al., 2018.)

2.5.3.4 Other surgical procedures

The risk for developing a PJI after a surgical procedure other than procedures involving the joint replacement seems to be low, even though there are case reports of PJIs occurring after genitourinary (Dabasia et al., 2009; Pepke et al., 2013) and gastrointestinal procedures (Cornelius et al., 2003; Schlaeffer et al., 1996; Triesenberg et al., 1992; Vanderhooft & Robinson, 1994).

In an older study, Ainscow et al. reported that of their cohort of 1 000 patients with a hip or knee replacement, 224 patients underwent a dental or other surgical procedure after the joint replacement, and none developed a PJI subsequently. None of these patients received antibiotic prophylaxis before the procedure. (Ainscow & Denham, 1984.) In addition, in a prospective case-control study, Gupta et al. showed that genitourinary procedures did not increase the risk for PJI (Gupta et al., 2015). In another study from the same study group, esophago-gastro-duodenoscopy with biopsy was associated with an increased risk for PJI, but other gastrointestinal procedures were not. Moreover, most of the PJIs were caused by pathogens not

associated with the gastrointestinal tract, and there was no difference in the microbiology of the PJIs between patients who had undergone a gastrointestinal procedure and those who had not. (Coelho-Prabhu et al., 2013.)

2.6 Prevention of periprosthetic joint infections

The measures used to prevent PJIs can be divided into different categories with respect to the timing of the surgery, similarly to the risk factors for PJI (Table 7). Preoperative measures are aimed at optimizing the patient's condition prior to surgery, peri- and intraoperative measures aim to prevent contamination of the wound and joint replacement, and postoperative measures are directed to prevent wound infection and improve wound healing. In addition, postoperative measures include prevention of hematogenous spreading from remote infections to the joint replacement.

The evidence to support the use of different preventive measures is varied, and the use of some preventive measures is under debate. In the most recent guideline on the prevention of SSIs, the CDC identified six key topics related specifically for the prevention of PJIs that were deemed unresolved and for which no recommendations could be made. These included blood transfusion, systemic immunosuppressive therapy, intra-articular corticosteroid injection, anticoagulation, orthopedic surgical space suit, postoperative antimicrobial prophylaxis duration with drain use and biofilm. (Berrios-Torres et al., 2017.) Other unresolved topics considered in the guideline development process but not included as priority guideline research topics were anesthesia, operating room environment and *S. aureus* nasal screening and decolonization (Berbari et al., 2017).

As the PJI rates have decreased thanks to effective peri- and intraoperative preventive methods, there has been a special interest to identify patient-related risk factors for PJI and to focus research on the prevention of PJIs to patient-optimization. This is especially important as the patients undergoing joint replacement surgery are more obese and have more comorbidities than before (Singh & Lewallen, 2014). However, it is unclear whether comprehensive risk-factor modifications would lead to decreased rates of PJIs (Everhart et al., 2016).

Table 7. Measures currently used to prevent periprosthetic joint infections with varying evidence base*

Preoperative measures	Perioperative measures	Intraoperative measures	Postoperative measures
Dental screening	Antibiotic prophylaxis	Antibiotic-impregnated cement	Avoidance of unnecessary blood transfusions
Glycemic control	Perioperative skin preparation with an alcohol-based antiseptic agent	Changing the scalpel after the skin incision	Minimizing the length of hospital stay
S.aureus nasal screening and decolonization		Keeping the duration of surgery to a minimum	Prevention of hematoma formation
Smoking cessation 4 weeks preoperatively		Laminar airflow	Use of antibiotic prophylaxis before (surgical) procedures
Treatment of active infections (especially in the operation area)		Maintenance of normothermia	
Weight loss (deferral of surgery for patients with BMI >40)		No extra personnel in the operating room	
Withholding immunosuppressive medication		Protective gear of the operating staff and use of body exhaust systems	

*, (Alaee et al., 2019; Berrios-Torres et al., 2017; Cizmic et al., 2019; Mangram et al., 1999; Marculescu et al., 2016; Rezapoor & Parvizi, 2015; Workgroup of the American Association of Hip and Knee Surgeons Evidence Based Committee, 2013)

2.6.1 Preoperative measures

Many of the preoperative measures to prevent PJIs are focused on modifiable patient-related risk factors, such as hyperglycemia and obesity (Rezapoor & Parvizi, 2015) and smoking cessation (Cizmic et al., 2019). These are based on variable levels of evidence, however, and well-conducted prospective studies are often lacking (Berbari et al., 2017). For example, the CDC has made a strong recommendation to control blood glucose levels preoperatively to prevent SSIs, but the recommendation is based on low quality evidence (Mangram et al., 1999). Furthermore, in an update to the CDC guidelines for the prevention of SSIs, no recommendation could be made on the optimal level for preoperative hemoglobin A1C, as no randomized studies exist on the topic (Berrios-Torres et al., 2017). On the other hand, guidelines suggest weight loss to obese patients to reduce the risk for developing a PJI, but the optimal method for preoperative weight loss is not known (Cizmic et al., 2019). In

addition, the American Association of Hip and Knee Surgeons recommends deferring joint replacement surgery for patients with BMI >40 (Workgroup of the American Association of Hip and Knee Surgeons Evidence Based Committee, 2013).

Treatment of active infections, including skin infections and UTIs, is recommended preoperatively to prevent subsequent PJIs (Cizmic et al., 2019). However, treatment of preoperative ASB with antibiotics has not been effective in preventing PJIs (Cordero-Ampuero et al., 2013; Lamb et al., 2016; Martinez-Velez et al., 2016; R. Sousa et al., 2014).

Currently, routine preoperative dental screening is recommended only for certain high-risk groups (e.g. patients with diabetes or rheumatic diseases, smokers, drinkers of carbonated beverages and those at a lower socioeconomic level) in the recent international consensus statement, as there are no prospective studies evaluating the effect of preoperative dental screening in reducing PJIs (Ares et al., 2019). On the other hand, the incidence of dental pathology in patients planned to undergo elective joint replacement surgery is fairly high, up to 23–29% (Barrington & Barrington, 2011; Vuorinen et al., 2018).

There is some controversy regarding preoperative nasal screening for *S.aureus* carriage and decolonization. As *S.aureus* carriage has been shown to be a risk factor for SSIs, it has been proposed that even in the absence of active infection, preoperative staphylococcal decolonization could reduce the incidence of SSIs caused by *S.aureus* (Chen et al., 2013; Schweizer et al., 2013; Stambough et al., 2017; Weiser & Moucha, 2015). However, it is not clear whether a universal decolonization regimen or a so-called "screen and treat" approach would be better, nor is the optimal decolonization method known.

Chen et al. showed a reduction in SSI rates for decolonization programs in a large meta-analysis. The studies included in the analysis were very heterogeneous, however, as some of the decolonization programs used only nasal mupirocin and some used nasal mupirocin in combination with chlorhexidine showers. Furthermore, some studies had universal decolonization programs, whereas in others, only patients screened positive for *S.aureus* carriage were decolonized. (Chen et al., 2013.) There have been studies that favor universal decolonization over "screen and treat" protocols in terms of efficiency and cost-effectiveness (Stambough et al., 2017). However, there have been concerns of increased antibiotic resistance following widespread use of mupirocin in the decolonization regimen. Thus no consensus on the decolonization regimens could be reached in the recent international consensus meeting (Akesson et al., 2019).

Oral antibiotics can reduce the carriage of *S.aureus* (Kumar et al., 2015), but the concentrations of oral antibiotics in the nares are not sufficient for effective decolonization (Peterson et al., 1990; Strausbaugh et al., 1992). Thus they are recommended to be used only in conjunction with topical agents in the decolonization of methicillin-resistant *S.aureus* (MRSA) (McConeghy et al., 2009; Simor et al., 2007). In addition, the routine use of oral antibiotics in MRSA decolonization regimens is discouraged by the IDSA due to concerns regarding increased antibiotic resistance (Liu et al., 2011). The use of oral antibiotics in decolonization regimens prior to joint replacement surgery has not been studied.

2.6.2 Peri- and intraoperative measures

One of the most effective methods to prevent PJIs is the use of perioperative antibiotic prophylaxis, and the number needed to treat (NNT) value for perioperative antibiotic prophylaxis in the prevention of SSIs for joint replacement surgery is low (AlBuhairan et al., 2008). An early study on antibiotic prophylaxis in joint replacement surgery showed a significant decrease in the incidence of deep infection from 3.3% to 0.9% when cefazolin was compared to placebo (Hill et al., 1981). The use of perioperative antibiotic prophylaxis has a well-established role in the prevention of PJIs and is recommended by the international consensus meeting and the American Academy of Orthopaedic Surgeons (Aboltins et al., 2019; American Academy of Orthopaedic Surgeons, 2014; Hansen et al., 2014). The key to successful administration of antibiotic prophylaxis is optimal timing and correct choice of antibiotics (van Kasteren et al., 2007). Currently, first or second generation cephalosporins are recommended (Hansen et al., 2014). There are concerns, however, of their efficacy if the carriage rate of resistant staphylococci in the population increases.

In addition to perioperative antibiotics, perioperative skin preparation is universally accepted as a means to prevent PJIs (Atkins et al., 2019; Berrios-Torres et al., 2017). The most effective antiseptic agent is not known, as studies have not managed to show superiority of one agent over others. The most commonly studied agents are povidone-iodine and chlorhexidine gluconate, either with or without isopropyl alcohol. The existing guidelines recommend the use of alcohol-based solutions unless contraindicated. (Atkins et al., 2019; Berrios-Torres et al., 2017.)

In a classic study, Hill et al. interestingly showed that the effect of perioperative antibiotics was nonsignificant if the intraoperative conditions were optimized (Hill

et al., 1981). Furthermore, the importance of intraoperative methods to reduce the risk for PJI was dramatically illustrated in another classic study by Charnley, where the incidence of PJI fell from 7% to 0,5% purely as a result of intraoperative methods to prevent contamination of the wound and joint replacement. The most important method was deemed to be the use of laminar airflow ventilation, but also the use of improved protective gear of the operating staff and improved methods of wound closure were assumed to play a role. (Charnley, 1972.) However, the results of these older studies may not apply in a modern day context, and in fact, there are more recent studies that have not shown any benefit in using laminar airflow ventilation or body exhaust systems in reducing the incidence of PJI (Breier et al., 2011). Furthermore, there are two studies from New Zealand that show an association between the use of laminar airflow ventilation and an increased risk for PJI (Hooper et al., 2011; Tayton et al., 2016). Yet, there is considerable variation in laminar airflow technologies used in different studies, and this might affect the results.

Prophylactic antibiotics can also be administered via the use of antibiotic-impregnated cement. Most commonly, vancomycin or aminoglycosides, such as tobramycin and gentamycin, are used. Again, the evidence supporting this practice is varied and no consensus could be reached in the international consensus meeting, even though the practice is widely used in many countries. (Fillingham et al., 2019.) On the other hand, in a study by Tayton et al., the use of antibiotic-impregnated cement was associated with a higher risk for PJI, but the results could have been confounded by the fact that antibiotic-cement may have been reserved for patients already at a higher risk for infection (Tayton et al., 2016). Thus, based on the lack of definitive evidence for the benefit of using antibiotic-impregnated cement in primary joint replacement surgery, it was suggested in the consensus statement that its use might be most justified in surgeries with a high risk for infection.

Other well-established methods to decrease the risk of contamination of the wound or the joint replacement include changing the scalpel after the skin incision and keeping the operating time to a minimum. Some of the more experimental methods include the use of antibiotic coatings on implants, but large-scale studies on these are lacking. (Alaee et al., 2019.) In addition to operating room conditions, also the maintenance of optimal patient condition is important, especially the maintenance of normothermia (Aalirezaie et al., 2019a).

2.6.3 Postoperative measures

Postoperative methods to decrease the risk for PJI in the immediate postoperative period are aimed at prevention of wound contamination/infection and improving wound healing. These include keeping the wound covered and dry for 48 hours postoperatively. There is also some evidence that the type of dressing used to cover the wound could have an effect on the risk for SSI and PJI, but more studies are needed, especially to evaluate the cost-effectiveness of using special dressings, such as ones with antiseptic or antimicrobial properties. (Al-Houraibi et al., 2019.)

In the long term, postoperative methods to prevent PJIs are aimed at preventing hematogenous spread from distant infectious foci to the replaced joint. These are mainly focused on the prevention of bacteremia, especially related to dental or other surgical procedures.

The need for subsequent antibiotic prophylaxis before dental procedures for patients with joint replacements has been under debate. Even though there are reports with PJIs caused by pathogens from the oral flora (Bartzokas et al., 1994; LaPorte et al., 1999), giving antibiotic prophylaxis before dental procedures for patients with joint replacements in order to prevent PJIs has not been effective in other studies (Ainscow & Denham, 1984; Berbari et al., 2010a; Kao et al., 2017), and therefore it is not routinely recommended by the American Dental Association (Sollecito et al., 2015) or the international consensus statement on PJIs (Arnold et al., 2019). However, maintaining good oral hygiene is recommended for patients with prosthetic joints (Arnold et al., 2019).

The issue of antibiotic prophylaxis before other surgical procedures not involving the joint replacement is not clear. There are few studies on the topic, and they are underpowered. Gupta et al. showed that prophylactic antibiotics before genitourinary procedures did not decrease the risk for PJI (Gupta et al., 2015). However, it should be noted that in that study, the proportion of patients receiving antibiotic prophylaxis was very low (2%), thus making definite conclusions on the efficacy of antibiotic prophylaxis difficult. Also, even though Coelho-Prabhu et al. showed an increased risk for PJI after esophago-gastro-duodenoscopy with biopsy, only 1% of the study patients had received prophylactic antibiotics before their gastrointestinal procedure and thus no conclusions on the efficacy of the prophylaxis could be made (Coelho-Prabhu et al., 2013). Therefore, giving antibiotic prophylaxis for patients with joint replacements before genitourinary or gastrointestinal procedures is not recommended by the recent international consensus statement (Arnold et al., 2019; Bravo et al., 2019) or by the American Society for

Gastrointestinal Endoscopy (ASGE Standards of Practice Committee et al., 2015). The American Urology Association does not recommend routine antibiotic prophylaxis for patients with joint replacements before urologic procedures, but they do recommend giving it for certain high-risk groups (such as during the first two years after joint replacement surgery and for immunocompromised patients) (Wolf et al., 2008).

3 AIMS OF THE STUDY

The aims of the present study were:

1) To compare the old CDC diagnostic criteria for PJI with the consensus meeting criteria from 2013 in patients with a suspected PJI and to examine possible reasons for discordance between the criteria sets (Study I)

2) To assess the effect of preoperative bacteriuria on the risk for PJI in a one-year follow-up (Study II)

3) To assess the effect of preoperative oral antibiotic use on the risk for PJI in a one-year follow-up (Study III)

4) To examine the risk for developing a PJI during an episode of bacteremia and to identify possible risk factors leading to it (Study IV)

4 SUBJECTS AND METHODS

4.1 Overview of the study

The retrospective study was conducted in the Coxa Hospital for Joint Replacement, Tampere, Finland. It is a publicly funded tertiary hospital dedicated to joint replacement surgery with a population base of ca. 500 000. It was founded in September 2002 and approximately 2 000–3 000 joint replacement surgeries are performed there annually (Järvelin et al., 2018). It is also a referral center for complications related to joint replacement surgery.

For Study I, patients from the Pirkanmaa Hospital District treated for a PJI of the hip or knee in the Coxa Hospital between 2002 and 2014 and with previous joint replacement surgery in 2013 or earlier (with no time limit) were identified. The primary joint replacements of the PJI patients could have been done in Coxa or in other hospitals. Time periods were chosen to have at least one year of follow-up for each joint replacement. Only patients with total joint replacements were considered.

Patient material in Studies II and III consisted of all patients undergoing a primary total hip or knee replacement in the Coxa hospital between September 2002 and December 2013. Study IV included patients from the Pirkanmaa Hospital District with a primary total hip or knee replacement performed in the Coxa hospital between September 2002 and December 2013. Each joint replacement was considered separately for patients with multiple primary joint replacements.

Follow-up periods were one year in Studies II and III and from 0 to 12 years in Study IV. An overview of the patient material used in the studies and study settings is given in Table 8.

Table 8. Overview of the study patients and settings

Study number	n (joint replacements)	Patients	Length of follow-up	Definition of a PJI	Primary outcome	Comments
I	NA	Patients from Pirkanmaa Hospital District treated for a PJI of the hip or knee in the Coxa hospital	NA	CDC and Consensus Meeting criteria	Fulfillment of either set of diagnostic criteria for PJI studied	405 cases of PJI identified
II	23 171	Patients with a primary joint replacement of the hip or knee performed in the Coxa hospital	1 year	CDC	Occurrence of a PJI	
III	23 171	Patients with a primary joint replacement of the hip or knee performed in the Coxa hospital	1 year	CDC	Occurrence of a PJI	
IV	19 262	Patients from Pirkanmaa Hospital District with a primary joint replacement of the hip or knee performed in the Coxa hospital	6 years (mean, range 0–12)	CDC and Consensus Meeting criteria	Occurrence of a PJI as a consequence of bacteremia	

4.2 Data sources

4.2.1 Identification of periprosthetic joint infection cases

In order to identify as many PJI cases as possible for Study I, six different data sources were used to identify possible cases of infection. Descriptions of each data source and how the data was combined are given below. As data for the whole study period (2002–2014) could not be gathered from all data sources, time periods for available data are given for each source. The same combined data of infection cases was also used in Study IV, except that PJIs occurring in joints not previously operated in the Coxa hospital were excluded.

For Studies II and III, all SSIs (including superficial and deep incisional infections and PJIs) were identified from the local healthcare-associated infection register of the Tampere University Hospital.

4.2.1.1 Finnish Hospital Infection Program

The Coxa hospital participates in the Finnish Hospital Infection Program (SIRO) of the National Institute for Health and Welfare. Data is prospectively collected from the participating hospitals according to the NNIS standards modified for Finland (Huotari et al., 2007b). SSI cases are classified according to the CDC criteria from 1992 (Horan et al., 1992). The follow-up time for each patient is one year post-operatively.

In order to identify SSI cases that occur after discharge, patients are given a questionnaire form where they can report problems related to wound healing. In previous studies from the Coxa hospital, it was shown that annual response rate of the questionnaires ranged from 71 to 83% (Jämsen, 2009). In addition, an infection control nurse is employed to identify SSIs that are treated in the Coxa Hospital.

PJI cases from the Coxa hospital in the Finnish Hospital Infection Program from 2005–2010 and 2012–2013 were identified. The Coxa hospital joined the surveillance program in 2005. The year 2011 is missing due to technical problems in data transfer.

4.2.1.2 Local healthcare-associated infection register of the Tampere University Hospital

Data gathered as part of the infection surveillance for the SIRO program is also recorded in the local healthcare-associated infection register of the Tampere University Hospital (SAI). The register is run by a team of infection control nurses and lead by a specialist in infectious diseases. PJI cases recorded in the register in 2002–2014 were identified.

SSI (including superficial, deep incisional infections and PJIs) cases recorded in the register within one year from primary surgery in 2002–2014 for patients with a primary knee or hip joint replacement performed in the Coxa hospital in 2002–2013 were identified for Studies II and III.

4.2.1.3 Microbial cultures from joint samples

Positive microbial cultures from synovial fluid or tissue samples taken in the Coxa hospital in 2002–2014 were retrieved from the electronic records of the microbiological laboratory (see Section 4.2.3 for more details).

4.2.1.4 Hospital discharge records

Information on patients requiring overnight treatment in the hospital is recorded in the hospital discharge records, including diagnosis codes. Patients in the Coxa hospital with a diagnosis code related to a PJI [ICD-10 diagnosis code T84.5 (Infection and inflammatory reaction due to internal joint prosthesis) or T81.4 (Infection following a procedure, not elsewhere classified)] in 2002–2014 were identified from the discharge records.

4.2.1.5 Local prospective joint replacement database

All revision joint replacements that were performed because of an infection in the Coxa Hospital, as recorded by the operating surgeon between 2002–2014, were identified from the local joint replacement database (TEKOSET).

The database is an electronic recording system designed to collect operative and outcome data on joint replacement surgery. Data is collected prospectively, and the

database covers preoperative, operative and postoperative data, including indications for surgery. (Jämsen, 2009.)

4.2.1.6 Hospital infection register

The Coxa Hospital has its own infection register that was established in 2012 for clinical purposes and to prospectively collect data on the quality of care. Data is recorded in the register by a dedicated nurse; however, it is not collected according to any official infection surveillance guidelines, but more on a case-by-case basis. All PJI cases recorded in the register in 2012–2014 were identified.

4.2.1.7 Combining the data and case verification

After all possible cases of PJI (n=1 425) were identified from the six different data sources, patient charts of each patient were reviewed by the author of this thesis (MH). Unclear cases (n=67) were also reviewed by two infectious diseases specialists. Patients from outside of the Pirkanmaa Hospital District area (n=403) were excluded immediately. Patient exclusion based on other reasons was done after reviewing the patient charts. The most common reasons for exclusion were superficial wound infections (recorded as such in the SSI surveillance and verified from the patient charts, n=218) and cases mistakenly recorded as infections in the hospital discharge records (n=177). Positive bacterial cultures (n=60) without infection were defined as a single positive bacterial culture without any other diagnostic criteria for infection, including the treating physician's opinion. In addition, early PJIs previously operated in another hospital (n=4) and cases outside the study period (n=27) were excluded. Other reasons for exclusion are shown in Figure 1.

An overview of the combined data is shown in Figure 1. It was verified from the patient charts that all included cases fulfilled at least one set of diagnostic criteria studied.

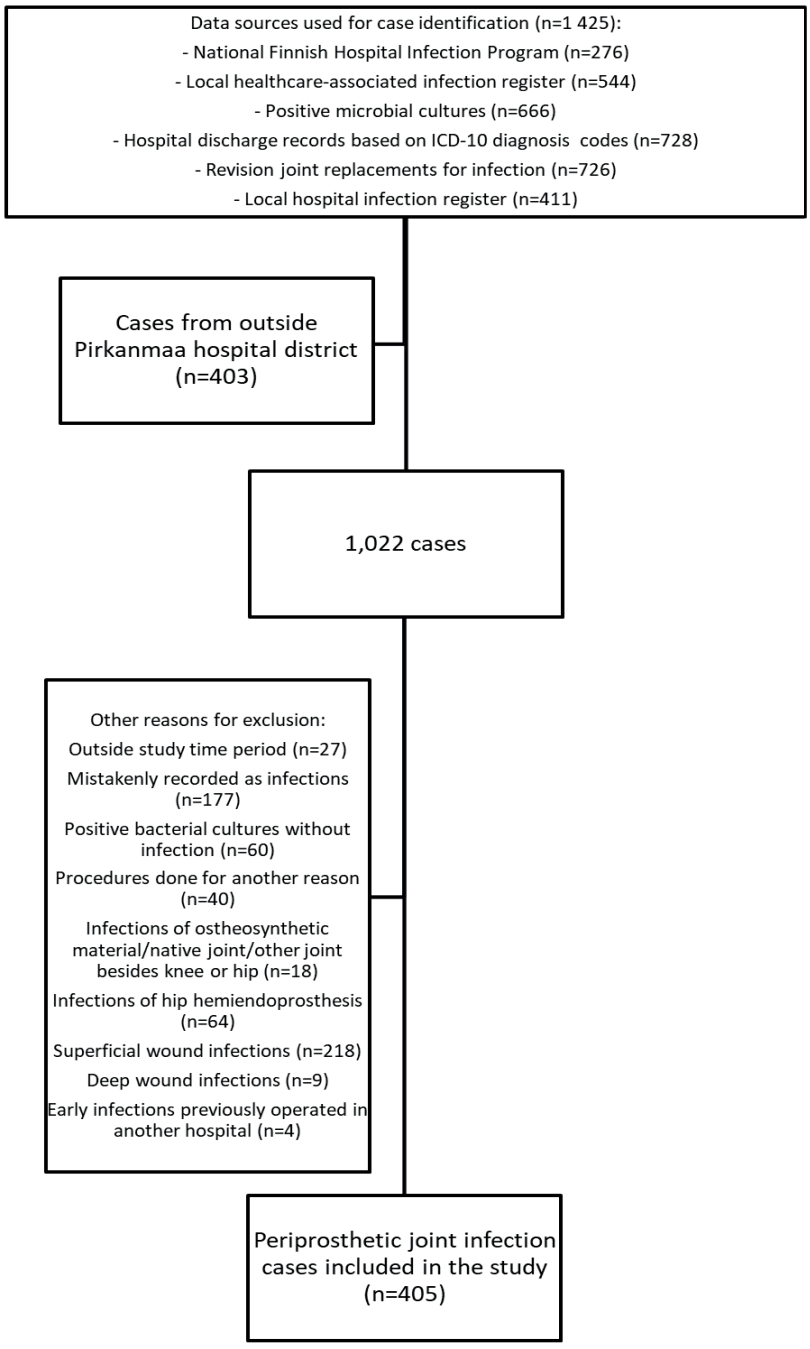

Figure 1. Overview of the patient data used in Study I

4.2.2 Drug registries of the Social Insurance Institution of Finland (Studies II – IV)

4.2.2.1 Drug reimbursement data

In Finland, patients with certain chronic illnesses are entitled to drug reimbursements for their medication. In order to receive reimbursements, the patient requires a certificate from the treating doctor. The right to reimbursements is granted based on specific diagnostic criteria for each disease, and with some diseases (e.g. hypertension) these criteria might differ from the criteria used to determine whether or not medication should be initiated. The Social Insurance Institution of Finland maintains a national drug reimbursement register, where special reimbursement codes and dates of entitlement are recorded for each person.

Patients with a valid right to reimbursement for diabetes, rheumatic diseases, hypertension, chronic heart failure, chronic coronary disease, arrhythmias, chronic lung disease, Parkinson's disease, epilepsy, Alzheimer's disease, psychotic disorders, hematological and solid malignancies at the time of their primary joint replacement surgery were identified from the national register. Chronic heart failure, chronic coronary disease and arrhythmias were grouped together for the analyses, as were Parkinson's disease, epilepsy, Alzheimer's disease and psychotic disorders. Data on comorbidities was used in Studies II–IV.

4.2.2.2 Preoperative oral antibiotics

Antibiotics are not available in Finland without a prescription from a doctor and all antibiotic purchases are recorded in a nationwide prescription register run by the Social Insurance Institution of Finland. It is commonly used for research purposes, as information on drug purchases can be easily retrieved. However, drugs given for in-patients are not recorded in the register. (Furu et al., 2010.)

The courses of antibiotics purchased by the patients within 90 days before the joint replacement surgery were identified from the prescription register for Studies II and III. The antibiotics were identified based on their Anatomical Therapeutic Chemical Classification System (ATC) codes (*WHO list of ATC codes*), and the type of antibiotic, number of packages and the date of purchase were recorded.

4.2.3 Microbiological data

All microbiological data was retrieved from the electronic records of the accredited microbiological laboratory of the Tampere University Hospital.

Positive microbial cultures from synovial fluid or tissue samples taken in the Coxa hospital in 2002–2014 that were used in Study I to identify PJI cases were also used in Studies II–IV to evaluate the causative pathogens for PJIs.

The results of preoperative urine samples taken within 90 days before elective joint replacement surgery were obtained (Study II). From positive samples, the species of bacteria found and their antibiotic susceptibility data were recorded. The sample taken closest to the date of operation was used in the analyses, if more than one sample was taken. All bacterial growth in the urine was considered significant, except when mixed bacterial flora was reported. If more than one bacterium was reported in the sample, they were all recorded.

Positive blood culture results of the study patients occurring after the first joint replacement surgery until December 2014 were obtained (Study IV). Positive blood cultures caused by low-virulence bacteria (i.e. CoNS, corynebacteria, micrococci or *Cutibacterium* species) were considered to be contaminants, unless there was growth on two blood culture bottles. Positive blood cultures by other pathogens were always considered significant.

4.2.4 Other data

Additional patient-related data was retrieved from the local hospital database (TEKOSET). This data included preoperative information (municipality of residence, the weight and the height of patients and the indication for surgery), operative information (use of antibiotic-impregnated cement in the operation) and postoperative information (revision surgeries and date of death). The data on weights and heights was used to calculate BMIs.

The official database of carriers of multidrug resistant microbes in Pirkanmaa Hospital District was used to identify MRSA carriers.

Prophylactic intravenous antibiotics were administered perioperatively prior to incision in all joint replacement surgeries, a single dose of 3 grams of cefuroxime was used unless contraindicated. If this was the case, then 900 milligrams of clindamycin or one gram of vancomycin was used. Known MRSA carriers were given cefuroxime and vancomycin. If cement was used in the operation, it was gentamicin-impregnated.

4.3 Definition of outcome

In Study I, each case of PJI was checked to see, which diagnostic criteria they fulfilled from the old CDC criteria for PJIs (Horan et al., 1992) and from the diagnostic criteria set defined in the international consensus statement from 2013 (Zmistowski et al., 2014). Either the day when the new criteria set were met or, if that did not happen, the day when treatment was started (usually the day of revision joint replacement) was defined as the date of the occurrence of infection. Data was collected on an electronic data collection form.

The primary outcome in Studies II and III was the occurrence of a PJI, identified from the local healthcare-associated infection register. The occurrence of any SSI (superficial, deep incisional or PJI) was considered to be a secondary outcome.

In Study IV, the primary outcome was a PJI as a consequence of bacteremia. This was identified, if the same organism was cultured from blood and from the affected joint, unless the PJI was determined to be the source of the bacteremia. The latter definition was based on the timing of symptom onset. For culture-negative PJIs in patients with bacteremia, patient charts were reviewed to find out if the PJI was determined by the treating clinician to be caused by the pathogen identified in the blood culture. In addition, if there was a duration of more than seven days between the positive blood culture and identification of the PJI, patient charts were checked to verify the association.

4.4 Statistical methods

Frequencies for different variables were calculated and cross tables formed to compare the different diagnostic criteria in the whole study material and in different clinical subgroups (Study I). Incidence rates (per 1 000 person-years) were calculated for bacteremias and PJIs in Study IV.

Means and standard deviations (SD) were calculated for continuous variables with a normal distribution and medians and range for variables with a skew distribution. Categorical variables were compared using χ^2 test and continuous variables with Student's independent-samples t-test.

To examine the association between positive urine cultures (Study II) and preoperative oral antibiotic use (Study III) and the outcome (PJIs and all SSIs separately), binary logistic regression with univariate analysis was used and ORs (odds ratios) and 95% CIs (confidence intervals) were calculated. Then, a

multivariable model was developed to account for confounding factors. Variables in the model included patients' gender, operated joint, age, BMI (only Study III), use of cement in the operation (only Study III), indication for surgery (osteoarthritis, rheumatic disease, previous trauma and other reasons) (only Study III) and chronic diseases (chronic heart disease, chronic lung disease, diabetes, hypertension, malignancy, neurological or psychiatric disorder and rheumatic disease). In Study III, a separate analysis was also performed for patients with antibiotics with potential activity against staphylococci (amoxicillin-clavulanate, cephalosporins, clindamycin, flucloxacillin, fluoroquinolones, macrolides, tetracyclines, trimethoprim and trimethoprim/sulfamethoxazole).

Binary logistic regression with univariate analysis was also used to examine the association between potential risk factors (number of bacteremias, BMI, male gender, knee location, time since previous joint replacement surgery, age, indication for joint replacement surgery, use of cement in the operation and chronic diseases) and the development of a PJI as a consequence of bacteremia in Study IV.

For Study III, variables associated with preoperative antibiotic use were used to calculate propensity scores. Patient matching was performed using nearest neighbour matching with caliper width 0.02 (0.2 of the standard deviation of the logit of the propensity score). This resulted in 4 106 matched pairs. A logistic regression analysis was performed in the matched patient population.

In all studies, a p-value <0.05 was considered statistically significant. All statistical analyses were performed using SPSS for Windows statistical software package versions 23.0 (Studies I–III) or 25.0 (Study IV).

4.5 Ethical considerations

Informed patient consent was not required according to the Finnish national legislation, as all data was retrospectively gathered from patient charts and registers. Permission to review patient charts was acquired from the heads of the Science Centre of the Pirkanmaa Hospital District and Coxa Hospital. A statement from the Ethical Review Board of the Pirkanmaa Hospital District was acquired.

All data analyses were performed using pseudonymized data and patient-identifiers were stored in a secure drive of the Pirkanmaa Hospital District.

Good clinical practice and the Helsinki Declaration were followed during the conduction of the study. The aims of the study were clinically relevant, and the study methods used were validated and well-known to the researchers.

5 SUMMARY OF THE RESULTS

The incidence of PJI was 0.68% (158/23 171 joint replacements) in a one-year follow-up after primary hip or knee replacement surgery (Studies II and III). For hip replacements, the incidence was 0.57% (58/10 200) and for knee replacements 0.77% (100/12 971). In total, there were 490 SSIs (2.11%), when also the superficial and deep incisional infections were included.

In the longer follow-up period (up to 12 years, Study IV) the incidence of PJI after primary joint replacement surgery was 1.50% (288/19 262) and the incidence rate was 3.3 per 1 000 person-years. Of these PJIs, 131 (45%) occurred within 90 days from previous surgery, 53 (18%) occurred within 3–12 months and 104 (36%) occurred after one year. The distribution of PJIs over time is shown in Figure 2.

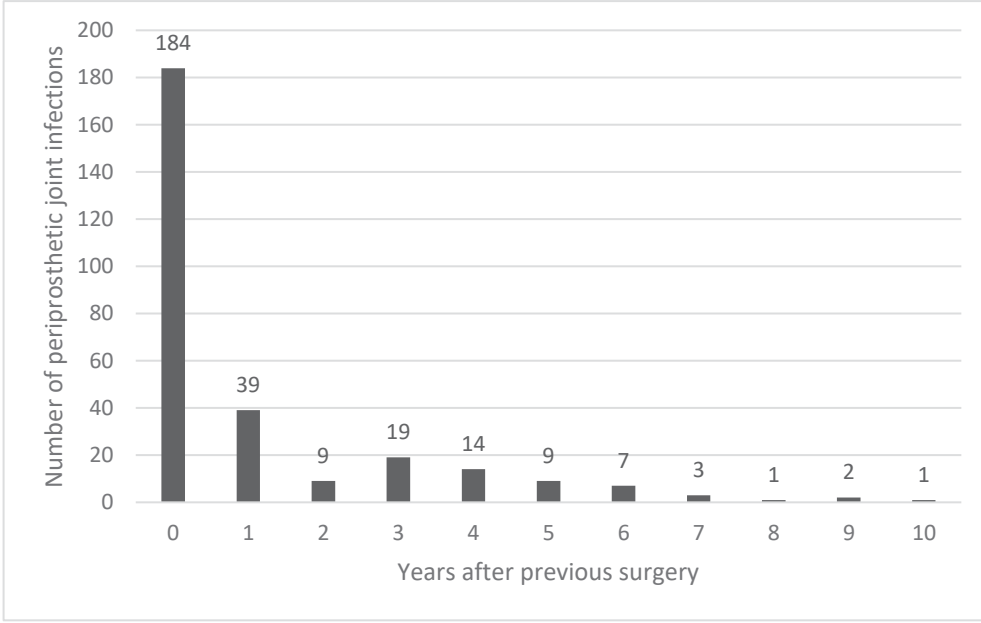

Figure 2. The distribution of periprosthetic joint infections over time

5.1 Concordance between diagnostic criteria for periprosthetic joint infections (Study I)

There was a notable difference in the incidence of PJI when two different sets of diagnostic criteria were used. Of the 405 PJI cases identified, 73 (18%) met only the old CDC criteria, but not the new consensus meeting criteria (Table 9). On the other hand, only one case (0.2%) fulfilled only the new set of criteria. The proportions of cases meeting the old and new criteria were similar when examined in different patient-related (gender and age), joint-related (location and previous operation) and infection-related (infection type and year of diagnosis) subgroups (Table 10). Ninety-one percent of patients with positive bacterial cultures met both sets of diagnostic criteria, as bacterial cultures are part of both sets of criteria.

Table 9. Number of cases meeting the old and new diagnostic criteria for periprosthetic joint infection

	N	% of all cases
CDC criteria from 1992		
Purulent drainage from a drain that is placed through a stab wound into the organ/space	0	0
Organisms isolated from an aseptically obtained culture of fluid or tissue in the organ/space	327	81
An abscess or other evidence of infection involving the organ/space that is found on direct examination, during reoperation, or by histopathologic or radiologic examination	38	9
Diagnosis of an organ/space SSI by a surgeon or attending physician	400	99
Total	404	100
Consensus meeting criteria from 2013		
Major criteria		
Two positive periprosthetic cultures with phenotypically identical organisms	239	59
A sinus tract communicating with the joint	82	20
Minor criteria		
Any three minor criteria	106	26
Elevated serum CRP and ESR*	199	49
Elevated synovial fluid WBC count or change on leukocyte esterase test strip†	192	47
Elevated synovial fluid PMN percentage‡	178	44
A single positive culture	88	22
Positive histological analysis of periprosthetic tissue	11	3
Total	332	82

*, CRP was measured from 402 patients, ESR from 152 patients and both from 152 patients. Early infections with an elevated CRP were considered to be fulfilling this criterion; †, Synovial fluid WBC was measured from 209 patients, leukocyte esterase test strips were not in use; ‡, Synovial fluid PMN% was measured from 198 patients

Table 10. Number of cases meeting the old and new diagnostic criteria for periprosthetic joint infection in different clinical subgroups

Subgroup	Cases	Cases fulfilling only the old CDC criteria		Cases fulfilling only the new consensus meeting criteria		Cases fulfilling both sets of criteria	
	n	n	%	n	%	n	%
All cases	405	73	18	1	0.2	331	82
Patient-related							
Gender							
Men	177	28	16	0	0	149	84
Women	228	45	20	1	0.4	182	80
Age							
≤70	195	37	19	0	0	158	81
>70	210	36	17	1	0.5	173	82
Joint-related							
Joints							
Hips	167	32	19	1	0.6	134	80
Knees	238	41	17	0	0	197	83
Previous operation							
Primary arthroplasty	285	48	17	1	0.4	236	83
Revision arthroplasty	120	25	21	0	0	95	79
Infection-related							
Infection type							
Early	151	24	16	1	0.7	126	83
Delayed	63	15	24	0	0	48	76
Late	191	34	18	0	0	157	82
Bacterial culture							
Positive	327	28	9	0	0	299	91
Negative	78	45	58	1	1.3	32	41
Infections diagnosed in							
2002–2006	97	29	30	0	0	68	70
2007–2010	165	20	12	0	0	145	88
2011–2014	143	24	17	1	0.7	118	83

When possible reasons for the discordance between the diagnostic criteria sets were examined, it was discovered that of the patients who did not fulfil the new criteria, 39 (53%) had their diagnosis based solely on the clinician's opinion. Fifteen (39%) of these patients fulfilled two of the minor criteria from the new criteria set. 16 (41%) had an increased number of leucocytes in the joint aspirate, 16 (41%) an increased number of polymorphonuclear cells, 13 (33%) had an elevated CRP and ESR value and 30 (77%) had an increased CRP value.

ESR was measured in 152 (38%) cases with a suspected PJI. If patients with a delayed or late PJI with an elevated CRP value, but whose ESR was not measured, were assumed to have an increased ESR, 169 patients would fulfil three or more minor criteria of the consensus meeting criteria. However, only 17 new infectious cases would be identified in total, as most of these patients also fulfilled either one of the main criteria. Of these new cases, 13 did not meet any other CDC criteria

besides the clinician's diagnosis. If they were considered to have a PJI according to the new criteria, there are still 26 (6%) cases in the whole study population, where the clinician's diagnosis is the only basis for the diagnosis of PJI.

There were 78 culture-negative cases. Of these, 58% (45/78) did not meet the new consensus meeting criteria for PJI. However, 38 (49%) fulfilled two minor criteria from the new criteria set. 38 (49%) had an increased number of leucocytes, 37 (47%) an increased number of polymorphonuclear cells in the joint aspirate, CRP and ESR were elevated in 38 (49%) of the patients and CRP was elevated in 58 (74%). Even though the number of intraoperative tissue samples taken increased over time, the proportion of culture-positive cases did not. Forty-nine (63%) of the culture-negative cases had four or more intraoperative samples.

5.2 Microbiology of periprosthetic joint infections

5.2.1 Early and delayed periprosthetic joint infections

The most common causative pathogens for PJIs during the first year after primary joint replacement surgery were *S.aureus* and CoNS (Table 11), with a slightly higher proportion of *S.aureus* during the first 3 months and a slightly higher proportion of CoNS 3–12 months after surgery. Streptococci were more common for delayed PJIs than for early infections. Gram-negative bacteria were found only in polymicrobial infections, most of which were early infections. Overall, 19% of the PJIs were culture-negative.

Table 11. The distribution of pathogens causing periprosthetic joint infections after primary joint replacement in a one-year follow-up

Pathogen	Early infections* (n=88)		Delayed infections† (n=70)	
	n	%	n	%
Gram-positive bacteria				
Staphylococcus aureus	26	30	17	24
Coagulase-negative staphylococci	22	25	20	29
Streptococci	7	8.0	11	16
Enterococci	1	1.1	0	0
Other gram-positive	2	2.3	2	2.9
Polymicrobial	15	17	1	1.4
Culture-negative	12	14	18	26
No cultures taken	3	3.4	1	1.4

*, Periprosthetic joint infections occurring within 3 months from surgery; †, Periprosthetic joint infections occurring 3–12 months from surgery

5.2.2 Periprosthetic joint infections as a consequence of bacteremia (Study IV)

There were 542 patients (out of 14 378, 3.8%) with at least one episode of bacteremia during the study period. Eighty-five (0.6%) patients had more than one bacteremia. Overall, there were 643 separate episodes of bacteremia. They occurred 3–4 285 days after the first joint replacement (median 1 460 days), and 85 (13%) occurred within one year. *E.coli* was the most common pathogen causing the bacteremias (241/643, 37% of bacteremias), followed by *S.aureus* (105, 16%), beta-hemolytic streptococci (58, 9%), *Streptococcus pneumoniae* (43, 7%), CoNS (28, 4%) and enterococci (28, 4%).

Seven percent (46/643) of the bacteremias resulted in a PJI, one of these was a bilateral knee infection. The development of a PJI as a consequence of bacteremia was most common for beta-hemolytic streptococci (21%, 12/58), *S.aureus* (20%, 21/105) and *viridans* group streptococci (16%, 4/25), but rare for gram-negative bacteria (1.3%, 4/314) (Figure 3). There were no PJIs related to bacteremias caused by CoNS.

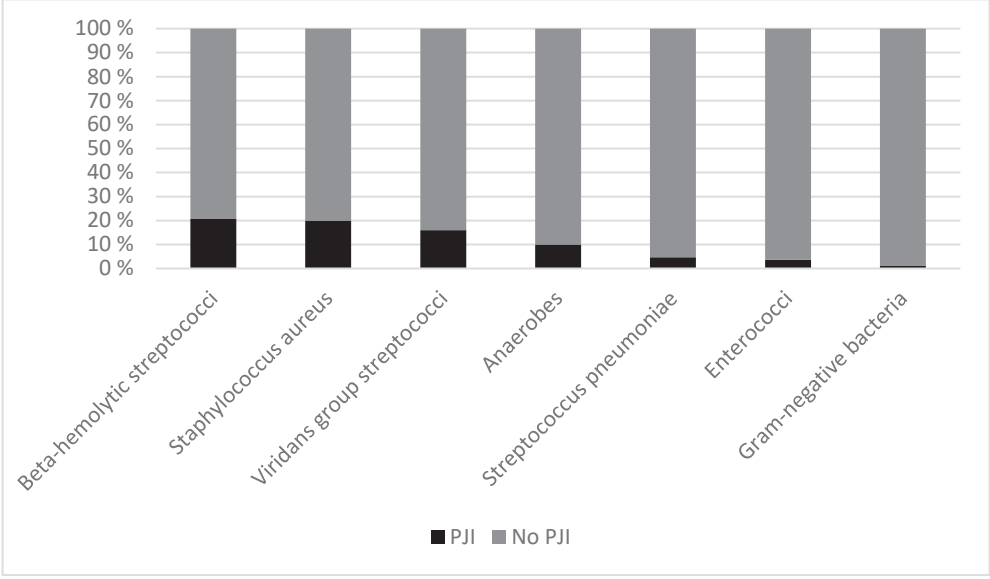

Figure 3. The risk for developing a periprosthetic joint infection (PJI) during bacteremia caused by different pathogens

5.3 Risk factors for periprosthetic joint infection (Study II, Study III, Study IV)

The distribution of characteristics of patients with primary joint replacement surgery and with and without PJI in a one-year follow-up is shown in Table 12. From the overall population, 62% (14 901/23 171) were female, 56% (12 971/23 171) had a knee replacement and the indication for surgery was osteoarthritis for 91% of the patients (21 005/23 171).

Table 12. The characteristics of patients with primary joint replacement surgery with and without periprosthetic joint infection (PJI)

Patient characteristic	Patients with PJI (n=158)		Patients without PJI (n=23 013)	
	n	%	n	%
Gender				
Male	86	54	8 724	38
Female	72	46	14 289	62
Replaced joint				
Hip	58	37	10 142	44
Knee	100	63	12 871	56
Indication for surgery				
Osteoarthritis	135	85	20 870	91
Rheumatoid arthritis	9	6	803	3
Trauma	10	6	742	3
Other	4	3	526	2
Unknown	0	0	72	0.3
Use of cement in the operation	123	78	17 827	77
Age, mean (SD)	69	11	67	11
Known MRSA-carrier*	1	0.6	61	0.2
Rural living location	26	17	3 116	14
Chronic comorbidities				
Chronic heart disease†	13	8	2 357	10
Chronic lung disease	11	7	1 504	7
Diabetes	20	13	1 857	8
Hypertension	35	22	6 281	27
Malignancy	3	2	804	3
Neurological or psychiatric disease‡	6	4	861	4
Rheumatic disease	5	3	1 207	5

*, Methicillin-resistant Staphylococcus aureus; †, Chronic heart failure, chronic coronary disease and arrhythmias; ‡, Parkinson's disease, epilepsy, Alzheimer's disease and psychotic disorders

5.3.1 Preoperative factors

Male gender, older age and diabetes were associated with an increased risk for PJI in a one-year follow-up in a univariate analysis (Table 13). Knee replacement also seemed to increase the risk, but this was not statistically significant. In the

multivariable analysis, male gender, knee replacement and older age were associated with an increased risk for PJI, the effect of diabetes was also almost statistically significant (Table 13). On the other hand, besides diabetes, other chronic comorbidities were not associated with an increased risk for PJI (Table 13).

The same preoperative risk factors that increased the risk for PJI also increased the overall risk for developing an SSI in the multivariable analysis: male gender (OR 1.45, 95% CI 1.19–1.77), knee replacement (OR 1.58, 95% CI 1.29–1.94) and older age (OR 1.01, 1.00–1.02). Diabetes, however, was not associated with an increased risk for SSI in the multivariable analysis (OR 1.09, 0.78–1.52).

Table 13. The effect of preoperative factors on the risk for periprosthetic joint infection

Factor	Univariate analysis		Multivariable analysis	
	OR	95% CI	OR	95% CI
Male gender	1.96	1.43–2.68	2.21	1.56–3.11
Knee replacement	1.36	0.98–1.88	1.43	1.01–2.04
Age	1.01	1.00–1.03	1.03	1.01–1.05
Positive urine culture	0.72	0.34–1.54	0.82	0.38–1.77
Chronic comorbidities				
Chronic heart disease	0.78	0.55–1.10	0.58	0.28–1.21
Chronic lung disease	1.07	0.58–1.98	1.04	0.53–2.05
Diabetes	1.65	1.03–2.65	1.64	0.99–2.73
Hypertension	0.76	0.52–1.11	1.09	0.50–2.38
Malignancy	0.54	0.17–1.68	0.55	0.17–1.72
Neurological or psychiatric disease†	1.02	0.45–2.30	1.15	0.51–2.63
Rheumatic disease	0.59	0.23–1.44	0.61	0.23–1.67

*, Chronic heart failure, chronic coronary disease and arrhythmias; †, Parkinson's disease, epilepsy, Alzheimer's disease and psychotic disorders

5.3.1.1 Preoperative bacteriuria

A preoperative urine sample was available in 87% (20 226/23 171) of primary joint replacement operations. Positive urine cultures were found in 1 378 samples (6.8%), 1 237 (90%) of these from women. Positive urine cultures were more common in older patients: mean age was 73 years (SD 10 years) for patients with bacteriuria and 67 years (SD 11 years) for patients without bacteriuria. Patients with positive urine cultures also had more chronic diseases than patients with negative urine cultures (Table 14).

Table 14. Comparison of chronic diseases in patients with positive and negative preoperative urine cultures

Chronic disease	Positive urine culture (n=1 378)		Negative urine culture (n=18 848)		
	n	%	n	%	p-value
Hypertension	491	36	5 138	27	<0.001
Diabetes	160	12	1 508	8	<0.001
Chronic heart disease*	159	12	1 947	10	0.16
Chronic lung disease	116	8	1 215	6	0.004
Rheumatic disease	97	7	959	5	0.002
Neurological or psychiatric disease†	85	6	662	4	<0.001
Malignancy	62	5	599	3	0.008

*, Chronic heart failure, chronic coronary disease and arrhythmias; †, Parkinson's disease, epilepsy, Alzheimer's disease and psychotic disorders

The incidence of PJI was 0.51% (7/1 378) for patients with a positive urine culture and 0.71% (133/18 848) for patients with a negative urine culture. Bacteriuria was not associated with an increased risk for PJI in the univariate or multivariable analysis (Table 13). In addition, there was no correlation between pathogens found in the preoperative urine samples and those causing the PJIs (Table 15). There was also no connection between bacteria found in the urine and those causing the superficial or deep wound infections.

Table 15. Description of patients with preoperative bacteriuria and periprosthetic joint infection

	Age	Gender	Joint	Time between urine sample and surgery (days)	Time between surgery and infection (days)	Treatment of bacteriuria with effective antibiotics	Pathogen found in urine	Pathogen causing PJI
1	81	Female	Hip	36	16	No	*Enterococcus faecalis*	*Staphylococcus aureus*
2	76	Female	Knee	9	16	Yes	*Escherichia coli*	NA*
3	76	Male	Knee	31	18	No	*Enterococcus faecalis*	Coagulase-negative staphylococcus
4	63	Female	Knee	11	36	No	*Klebsiella pneumoniae*	*Staphylococcus aureus*
5	81	Female	Knee	64	85	No	*Escherichia coli*	Coagulase-negative staphylococcus
6	75	Female	Knee	0	142	No	*Escherichia coli*	NA*
7	79	Male	Knee	29	258	No	Coagulase-negative staphylococcus	*Staphylococcus epidermidis*†

*, Culture-negative PJI; †, Different antibiogram from the strain found in the urine

Among the 2 945 patients with a missing urine sample, there were 18 cases of PJI (0.61%). The overall incidence of SSI was 1.8% (53/2 945). These incidences were similar to the incidences in the whole study population. In the 11 cases where the pathogen causing the PJI could be identified (*S.aureus*, Corynebacterium species and CoNS), no typical urinary tract pathogens were found.

5.3.2 Risk factors for hematogenous periprosthetic joint infections

Chronic comorbidities, gender or obesity did not affect the risk for developing a PJI during bacteremia (Table 16). Older age was associated with a lower risk for developing a PJI, but when the effect of *E.coli* bacteremias was examined in a multivariable analysis, this was no longer statistically significant (OR 0.97, 95% CI 0.95–1.00). There were also no joint-related factors (indication for primary surgery, joint location, time since previous surgery or use of cement in the primary operation) that affected the risk for developing a PJI during bacteremia.

On the other hand, having several bacteremias during the study period increased the risk for developing a PJI as a consequence of bacteremia (Table 16). Furthermore, the risk for developing a PJI was higher for bacteremias occurring within a year from previous surgery than for bacteremias occurring later.

Table 16. Potential risk factors for developing a periprosthetic joint infection (PJI) as a consequence of bacteremia

Risk factor	Joints with PJI (n=47)	Joints without PJI (n=672)		
	n (%)	n (%)	OR	95% CI
Patient characteristics				
Age at the time of bacteremia, y, mean (standard deviation)*	71 (11)	76 (10)	0.97	0.94–0.99
Body mass index ≥25	38 (81)	473 (70)	1.82	0.70–4.72
Chronic heart disease	6 (13)	72 (11)	1.22	0.50–2.97
Chronic lung disease	3 (6)	33 (5)	1.32	0.39–4.48
Diabetes	5 (11)	103 (15)	0.66	0.25–1.70
Male gender	21 (45)	276 (41)	1.16	0.64–2.10
Rheumatic disease	3 (6)	59 (9)	0.71	0.21–2.35
Joint-related				
Osteoarthritis as indication for primary operation	43 (92)	588 (88)	0.65	0.23–1.86
Knee location	29 (62)	398 (59)	1.11	0.60–2.04
Time since previous joint replacement (years)*				
<1	17 (36)	94 (12)	1.00	
1–10	28 (60)	672 (85)	0.23	0.12–0.44
>10	2 (4)	24 (3)	0.46	0.10–2.13
Use of cement in the primary operation	35 (74)	555 (83)	0.59	0.30–1.17
Other				
Number of bacteremias ≥2	13 (28)	96 (14)	2.29	1.17–4.50

*, Calculated for each bacteremia and joint (n=837) separately

5.4 Prevention of periprosthetic joint infections

5.4.1 Treatment of preoperative bacteriuria (Study II)

Twenty-five percent (344/1 378) of the patients with preoperative bacteriuria received antibiotics after the urine sample was taken. Of these, the prescribed antibiotic was not effective against the pathogen found in the urine in 51 cases. Thus, 293 (21%) patients with bacteriuria received effective antibiotic treatment.

One patient (0.34%) with effective antibiotic treatment for bacteriuria had a PJI in a one-year follow-up, whereas six patients out of 1 085 (0.55%) with bacteriuria, but no (effective) antibiotic treatment, had a PJI. Treating preoperative bacteriuria with effective antibiotics did not affect the risk for developing a PJI (OR 0.62, 95% CI 0.07–5.14).

5.4.2 Preoperative antibiotic use (Study III)

Overall, 18% (4 106/23 171) of the primary joint replacement operations were preceded by at least one course of antibiotics within 90 days before the operation. In 4.3% (989) operations there was more than one course of antibiotics. The distribution of time difference between the surgery and the purchase of the antibiotic course closest to the surgery is shown in Figure 4, the median number of days was 30.

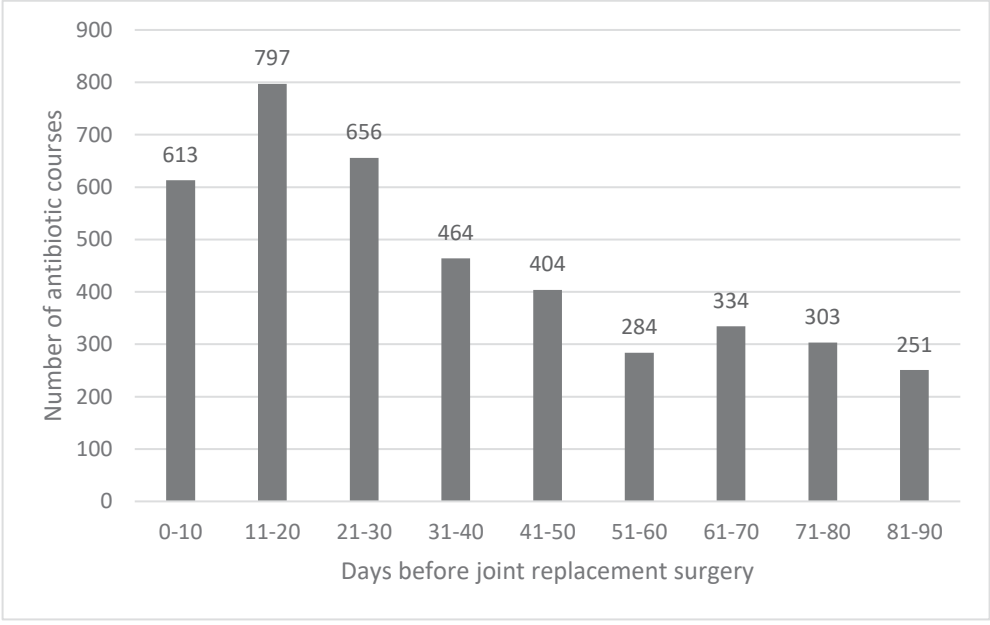

Figure 4. The distribution of time (in days) between the joint replacement and the purchase of antibiotics (the antibiotic course closest to the surgery)

First-generation cephalosporins, penicillin and pivmecillinam were the most commonly prescribed antibiotics (Table 17). Overall, the number of preoperatively purchased packages of antibiotics was 5 741, and the average antibiotic consumption was 2.75 packages per 1 000 patients per day.

Table 17. The most commonly used groups of antibiotics before elective joint replacement surgery

Antibiotic group	Number of operations preceded by antibiotic	
	n	% (of all operations)
First-generation cephalosporins	984	4.2
Penicillin	693	3.0
Pivmecillinam	571	2.5
Amoxicillin	544	2.3
Fluoroquinolones	500	2.2
Tetracyclines	424	1.8
Macrolides	374	1.6
Trimethoprim	303	1.3
Amoxicillin-clavulanate	182	0.8
Clindamycin	146	0.6

For patients with preoperative oral antibiotic use, the incidence of PJI was 0.29% (12/4 106), and for patients without antibiotic use, the incidence was 0.77% (146/19 065). The use of oral antibiotics within 30 days and 90 days before joint replacement surgery was associated with a lower risk for subsequent PJI in a univariate analysis (Table 18). The results remained statistically significant also in the multivariable analysis for antibiotic use 30 days preoperatively (OR 0.24, 95% CI 0.08–0.77) and 90 days preoperatively (OR 0.40, 95% CI 0.22–0.73). No individual antibiotic or antibiotic group decreased the risk statistically significantly (Table 18). The risk for PJI was statistically significantly decreased for patients with the use of anti-staphylococcal antibiotics (OR 0.34, 95% CI 0.16–0.72), when compared to patients without preoperative antibiotics, but not for patients with the use of other antibiotics (OR 0.46, 95% CI 0.19–1.13).

Table 18. The effect of preoperative oral antibiotic use on the risk for developing a periprosthetic joint infection (PJI)

Antibiotic use	Univariate analysis	
	OR	95% CI
Antibiotic use 30 days preoperatively	0.26	0.10–0.71
Antibiotic use 90 days preoperatively	0.38	0.21–0.69
The effect of individual antibiotic groups		
Amoxicillin	0.53	0.13–2.15
Amoxicillin-clavulanate	NA*	NA*
Clindamycin	1.01	0.14–7.23
First-generation cephalosporins	0.29	0.07–1.16
Fluoroquinolones	0.58	0.14–2.35
Macrolides	0.78	0.19–3.16
Penicillin	0.41	0.10–1.67
Pivmecillinam	0.51	0.13–2.05
Tetracyclines	NA*	NA*
Trimethoprim	NA*	NA*

*, There were no PJIs in this group

The use of preoperative oral antibiotics decreased the risk for PJI in different subgroup analyses as well. Results were similar when the operated joint (hip joint OR 0.36, 95% CI 0.13–1.00, knee joint OR 0.38, 95% CI 0.19–0.79), use of cement in the operation (cement used OR 0.40, 95% CI 0.21–0.77, cement not used or not known OR 0.29, 95% CI 0.07–1.22) and indication for surgery (osteoarthritis OR 0.37, 95% CI 0.17–0.70, other indications OR 0.47, 95% CI 0.11–1.99) were considered. However, due to insufficient statistical power, the results were not statistically significant in some subgroups.

The use of preoperative antibiotics 90 days preoperatively did not have an effect on the overall risk for SSI. The incidence of SSI was 1.90% (78/4 106) for patients with antibiotics and 2.16% (412/19 065) for patients without antibiotics (OR 0.88, 95% CI 0.69–1.12).

6 DISCUSSION

6.1 Diagnostic criteria for periprosthetic joint infection

There was notable discordance between the old CDC criteria and the consensus meeting diagnostic criteria for PJI from 2013 in Study I: one fifth of the PJI cases were identified as such only by the old criteria, but not the newer ones. Mainly the reason for this was that many of the cases identified as PJIs only by the treating clinician failed to meet the new, more objective, diagnostic criteria. Thus, different numbers of PJIs are identified by the different sets of criteria and the incidence of PJI is slightly lower when the new criteria are used.

The new diagnostic criteria were created in 2013 as an attempt to provide a gold standard for the diagnosis of PJI that could be used in research work and infection surveillance. However, they have not been validated, and neither have there been any previous studies comparing the old and new sets of criteria. The results of Study I raise two important points. Firstly, there is a possibility that some PJI cases could be missed by the new diagnostic criteria, as such a large proportion of patients with PJIs according to the old criteria did not meet them. It is possible that unnecessarily strict diagnostic criteria could miss some PJI cases if the diagnostic resources used in clinical work are not sufficient in a hospital. Secondly, it is possible that some of the PJIs identified by the old criteria were in fact not infected. These questions are important to keep in mind when assessing surveillance numbers, especially from different time periods.

Even though it can be questioned whether the 10% of the PJI cases where the diagnosis was based solely on the clinician's opinion were truly infected, it is likely that at least some of these cases are nevertheless true PJIs. In some of these cases, the failure to meet three minor criteria from the new criteria set was because ESR was not measured, as CRP is generally the preferred inflammatory marker in Finland. In fact, the utility of measuring both CRP and ESR as markers of PJI is not clear. Ghanem et al. showed a lower sensitivity of using CRP and ESR in combination as a marker for PJI, when compared to using either one alone (Ghanem et al., 2009). Furthermore, Johnson et al. showed that the same sensitivity was obtained when CRP alone or CRP and ESR in combination were used to diagnose PJI of the knee,

but the combination resulted in a significant increase in the number of false negative cases (from 5.3% to 11.1%) (Johnson et al., 2011). Cases of PJIs with normal CRP and ESR have also been reported (McArthur et al., 2015). Thus, requiring both CRP and ESR for the diagnosis of PJI is likely not needed and this is indeed reflected in the newest set of proposed diagnostic criteria, where they are included separately and also given different weights (Parvizi et al., 2018; Shohat et al., 2019).

Another reason for failing to meet the new diagnostic criteria could be the cut-off levels for synovial fluid leucocytes and polymorphonuclear cells. The accuracy of the determined cut-off levels can be questioned, as they are based on a small number of studies that have variable results (Zmistowski et al., 2014). Furthermore, high sensitivity and specificity for lower cut-off values, ranging from 1 100–3 450 for leucocytes and 64%–78% for PMN%, have been reported (Cipriano et al., 2012; Dinneen et al., 2013; Ghanem et al., 2008; Trampuz et al., 2004). Using lower cut-off values would have probably resulted in more patients being identified as having a PJI according to the new criteria as well.

Nevertheless, it is likely that some of the cases reported as PJIs according to the clinician's opinion were not truly infected, but could have for example represented adverse reactions to metal debris from metal-on-metal hip replacements (Judd & Noiseux, 2011; Mikhael et al., 2009; Wyles et al., 2013). These cases have been erroneously diagnosed as PJI, before the phenomenon was recognized. Unfortunately, in the study population of Study I, the types of joint replacements were not recorded and thus the number of metal-on-metal joint replacements is not known.

The results of Study I also show the importance of a positive bacterial culture in the diagnosis of a PJI. In total, about 80% of patients had at least one positive bacterial culture and almost 60% had at least two. This was also the most commonly fulfilled part of the new consensus meeting criteria. Indeed, bacterial cultures have a well-established role in the diagnosis of a PJI, and two positive cultures with the same organism is enough to make a diagnosis of a PJI also according to the newest set of diagnostic criteria (Parvizi et al., 2018). There has still been some debate about the optimal number of samples that should be taken and also about the number of positive samples required for the diagnosis of a PJI. Even though most recent studies have shown that four samples might be the optimal number in terms of sensitivity and specificity (Bemer et al., 2016; Gandhi et al., 2017; Peel et al., 2016), almost two thirds of the culture negative cases in Study I had four or more samples taken.

The importance of positive bacterial cultures in the diagnostic criteria for PJI is also shown by the fact that almost two thirds of the culture negative patients in Study

I met only the old CDC criteria. However, it is possible that some true culture negative PJIs were missed by the new criteria, as almost half of the culture negative cases met two other minor criteria. Thus, with a single positive bacterial culture, these patients would have been diagnosed as having a PJI also according to the new consensus meeting criteria. One possible reason for false negative bacterial cultures in PJI cases can be preceding antibiotic use (Berbari et al., 2007; Malekzadeh et al., 2010), but unfortunately this information could not be attained for the study population in Study I.

It should be acknowledged that the old CDC criteria were intended to be used for surveillance programs for a limited time period postoperatively, but Study I included patients that had been operated several years before. However, the number of patients identified by the two sets of diagnostic criteria were similar irrespective of the type of infection (early, delayed or late), suggesting that both criteria can also be applied for the diagnosis of late PJIs.

There is a shift, especially in terms of research and surveillance purposes, from a subjective diagnosis of a PJI relying only on the clinician's opinion to a diagnosis that is based on objective measurements. However, in clinical work, the diagnosis made by the clinician is still important and the new diagnostic criteria are not intended for clinical work as such. Nevertheless, a need for objective and uniform diagnostic criteria for PJI that can be used both in research and surveillance programs still remains.

6.2 Risk factors for periprosthetic joint infection

6.2.1 Preoperative bacteriuria

Study II shows that there is no association between preoperative bacteriuria and subsequent SSI or PJI, even with the effect of chronic diseases taken into account. In addition, there was no connection between pathogens found in the preoperative urine samples and pathogens causing postoperative SSIs.

The results of Study II are in line with many earlier studies (Berbari et al., 1998; Glynn & Sheehan, 1984; Ritter & Fechtman, 1987). In the classic study by Glynn and Sheehan (Glynn & Sheehan, 1984), preoperative bacteriuria was not associated with an increased risk for PJI, but the sample size of the study was very small and the follow-up period only three months. In fact, there were no PJIs in the whole

study population regardless of whether they had bacteriuria or not, thus making any definite conclusions impossible. A more recent study has also shown the lack of association between preoperative bacteriuria and subsequent PJI for hip joint replacements, but its reliability is again limited by a small sample size (Cordero-Ampuero et al., 2013). In addition, none of the above-mentioned studies have taken into account the possible confounding effect of chronic diseases.

There are other studies, however, where an association between preoperative bacteriuria and subsequent PJI has been found, even though no direct seeding from preoperative bacteriuria to the replaced joint has been reported (Ollivere et al., 2009; Sousa et al., 2014; Weale et al., 2019). Of these, studies by Sousa et al. and Weale et al. have larger sample sizes than other studies, but they are still considerably smaller than Study II, and especially the number of PJIs is considerably lower (Figure 5). Only in the study by Sousa et al. is there an attempt to take into account the effect of chronic diseases using a multivariable analysis, but this is not done very extensively, as only diabetes and obesity were included, in addition to the ASA score.

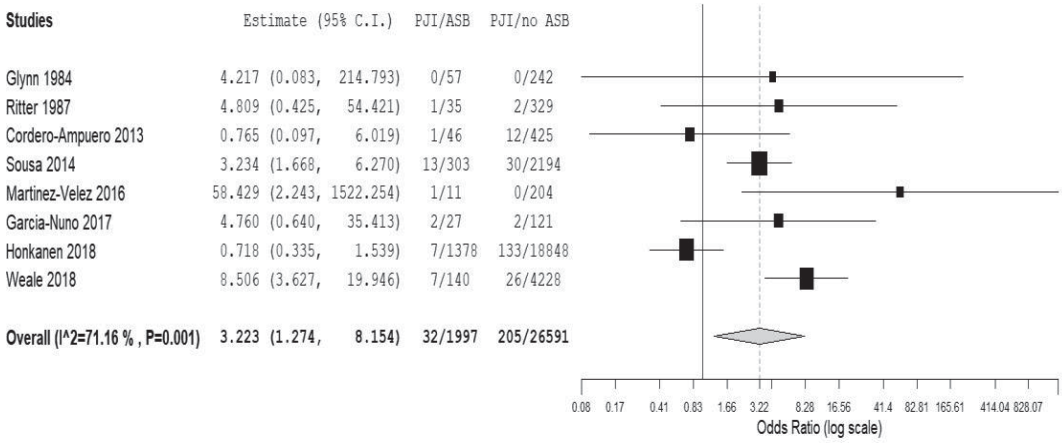

Figure 5. The results of studies on the effect of preoperative bacteriuria on the risk for periprosthetic joint infection (including Study II) (Cordero-Ampuero et al., 2013; Garcia-Nuno et al., 2017; Glynn & Sheehan, 1984; Martinez-Velez et al., 2016; Ritter & Fechtman, 1987; Sousa et al., 2014; Weale et al., 2019)

Since the publication of Study II, two meta-analyses have been published on the effect of preoperative bacteriuria on the risk for SSI and PJI (Gomez-Ochoa et al., 2019; Sousa et al., 2019). Interestingly, both of these show an increased risk for infection in patients with bacteriuria. However, there is moderate heterogeneity among the studies included in the analyses, reflecting the conflicting results found in different studies. This can also be seen in Figure 5, which includes the studies in the meta-analysis by Sousa et al., but with corrected numbers. Sousa et al. have misinterpreted the results of the study by Glynn and Sheehan, as this older study does not have any PJIs in either group, but Sousa et al. report two PJIs in the bacteriuria group. In addition, the ORs for individual studies reported in the meta-analysis by Sousa et al. are not correct, even though the overall OR has been calculated correctly. Despite the results of these meta-analyses, they both conclude that preoperative bacteriuria is probably a surrogate marker for some other unknown factor that is associated with an increased risk for PJI. On the other hand, it can be stated that the effect of possible confounding factors is taken into account most extensively in Study II when compared to the other studies and that patients with positive urine cultures have more chronic diseases than patients with negative ones.

Finally, screening for preoperative bacteriuria before joint replacement surgery is not recommended by the most recent consensus meeting statement either (Ares et al., 2019), even though the varied results of different studies are acknowledged. The results of Study II are also referred to and can be seen to validate this conclusion even further.

6.2.2 Risk factors for hematogenous periprosthetic joint infections

The overall rate of developing a PJI as a consequence of bacteremia in Study IV, seven percent, corresponds with the results of Uçkay et al. In their study, 6% of bacteremias lead to the development of a PJI (Uçkay et al., 2009), but the overall number of bacteremias (n=81) was considerably lower than in Study IV. There are no other studies evaluating the rate of PJIs during bacteremia, except for SAB. Previous studies focusing on the risk of PJI during SAB have reported somewhat higher rates than in Study IV (Lalani et al., 2008; Murdoch et al., 2001; Sendi et al., 2011).

The most important factor influencing the risk for developing a PJI as a consequence of bacteremia in Study IV seemed to be the pathogen causing the bacteremia. There have not been any studies examining this previously. It can be

calculated from the results of Uçkay et al. that in their small study, the rate of PJI was 2.9% for bacteremia caused by *E.coli*, 14% for *S.aureus* and 40% for anaerobes. But as the number of PJIs as a consequence of bacteremia was only five, it is impossible to make any relevant conclusions from their results. The high risk related to SAB has been known before, but interestingly, the risk was as high for beta-hemolytic streptococci as well in Study IV. Nevertheless, this can be expected, as beta-hemolytic streptococci have been reported to be important pathogens causing late hematogenous PJIs (Ainscow & Denham, 1984; Rodriguez et al., 2010; Stefánsdóttir et al., 2009). On the other hand, even though coagulase-negative staphylococci are important pathogens causing PJIs, surprisingly there were no PJIs during bacteremias caused by them in Study IV. There is evidence that nosocomial SABs are not associated with PJIs (Sendi et al., 2011; Tande et al., 2016), and as CoNS bacteremias are mostly nosocomial (Hitzenbichler et al., 2017), it is probable that these are not associated with PJIs either. Unfortunately, it was not possible to differentiate between nosocomial and community-acquired bacteremias in Study IV.

Even though *E.coli* was the most common pathogen causing bacteremias in Study IV by far, particularly in the oldest age groups, the development of a PJI as a consequence of *E.coli* bacterermia was rare. Hence, such particular attention with regards to the development of a PJI does not need to be paid to patients with bacteremias caused by gram-negative bacteria when compared to SABs or bacteremias by beta-hemolytic streptococci.

Different chronic diseases did not affect the risk of developing a hematogenous PJI in Study IV. Patient-related risk factors for hematogenous PJIs have not been identified in previous studies either (Sendi et al., 2011; Uçkay et al., 2009). Yet, multiple episodes of bacteremia were associated with an increased risk of PJI in Study IV, suggesting that there could be some unidentified factor predisposing the patients to infections in general. Nevertheless, rheumatic diseases or diabetes were not associated with an increased risk of developing a PJI during bacteremia.

Importantly, the risk of developing a PJI during bacteremia was highest during the first year after previous surgery. Often, early PJIs have been categorically classified as non-hematogenous, but Study IV shows that even very early PJIs can be the result of a bacteremia and not vice versa, as most of the pathogens in these cases were not typical bacteria causing primary PJIs. Thus, the increased risk for PJI during the first two years after surgery, observed in previous large studies (Kurtz et al., 2010; Ong et al., 2009; Pulido et al., 2008), is possibly partly due to the increased risk for hematogenous PJIs. Still, there are studies such as the one by Rakow et al.,

where most of the hematogenous PJIs occurred at a later occasion (Rakow et al., 2019).

6.3 Prevention of periprosthetic joint infections

6.3.1 Treatment of preoperative bacteriuria

Study II shows that treating preoperative bacteriuria with effective antibiotics does not have an effect on the risk for subsequent PJI. Other studies have not found any benefit in treating preoperative bacteriuria either, but the number of patients in many of the studies is very low (Table 19) (Cordero-Ampuero et al., 2013; Martinez-Velez et al., 2016; Sousa et al., 2014). It is interesting that even though Sousa et al. found a significant association between preoperative bacteriuria and risk for PJI, treating the bacteriuria did not have an effect on the risk for infection (Sousa et al., 2014). This seems to further support the assumption that preoperative bacteriuria is indeed a surrogate marker for some other factor related to the increased risk for PJI.

Table 19. The effect of treating preoperative bacteriuria on the risk for periprosthetic joint infection (PJI) (Cordero-Ampuero et al., 2013; Martinez-Velez et al., 2016; Sousa et al., 2014)

Study	PJI/treated bacteriuria		PJI/untreated bacteriuria		Effect of treatment	
	Number	%	Number	%	OR	95% CI
Cordero-Ampuero et al.	1/26	3.8	0/20	0	2.41	0.09–62.39
Sousa et al.	6/154	3.9	7/149	4.7	0.82	0.27–2.51
Martinez-Velez et al.	1/4	25	0/7	0	6.43	0.21–201.07
Honkanen et al. (Study II)	1/293	0.3	6/1 085	0.6	0.62	0.07–5.14

An interventional study by Lamb et al. showed that implementing a policy of not routinely screening preoperative urine samples led to a substantial decrease in the number of antibiotic prescriptions for preoperative bacteriuria as well, with no significant increase in the intervention period PJI rates (Lamb et al., 2016). This further supports the evidence that treatment of ASB preoperatively is not necessary, even though the study is limited by the remarkably low baseline PJI rate and the fact that outpatient antibiotic use could not be assessed.

Based on the evidence found in previous studies, including Study II, the recent international consensus meeting statement advices against treatment of preoperative asymptomatic bacteriuria (Ares et al., 2019). It can be seen in Table 20 that the patient material in Study II is the largest one to support this recommendation. It

should be noted that even though treatment of preoperative bacteriuria was supposedly routine practice at the time of the study period, only about one fifth of the patients with bacteriuria received effective antibiotics targeted to the pathogen found in the urine.

6.3.2 Preoperative antibiotic use

The overall use of oral antibiotics before elective joint replacement surgery has not really been studied before. In a Swedish study evaluating the bacterial colonization of patients planned for elective joint replacement surgery, it was found that 25% of the study patients had received antibiotics within six months before surgery (Stefánsdóttir et al., 2013). This is similar to the results of Study III, where almost one fifth of the patients had received at least one course of antibiotics within three months before surgery. In fact, the results seem to indicate that patients coming for elective joint replacement surgery receive more antibiotics than the general population. The antibiotic consumption of the study patients in Study III was 2.75 packages per 1 000 patients per day, whereas in recent years it has been about 2 packages per 1 000 patients per day in the overall population in Finland (Summary of the latest data on antibiotic consumption in the European Union, 2016).

Another, and perhaps more significant, finding of Study III is the association between preoperative oral antibiotic use and a decreased risk for subsequent PJI. This topic has not been studied before and therefore it is a novel finding. Possible explanations for the association are not completely clear. Even though treatment of active preoperative infections is generally accepted, and even recommended, as a means to prevent PJIs (Aggarwal et al., 2014), it should not offer any additional prophylactic protection against PJIs. In addition, active infections would probably lead to postponement of surgery.

As the use of antibiotics with activity against staphylococci seemed to be mostly responsible for the reduction in the incidence of PJI, it can be speculated that perhaps it had an effect on the frequency of *S.aureus* carriage. Nasal carriage of *S.aureus* is common: 25% to 40% of the general population are carriers (Kumar et al., 2015; Weiser & Moucha, 2015) and the situation is similar among patients planned for elective joint replacement surgery (Chen et al., 2013; Stefánsdóttir et al., 2013). On the other hand, nasal carriage of *S.aureus* is an independent risk factor for developing a SSI after joint replacement surgery (Kalmeijer et al., 2000) and thus

different decolonization programs have been proposed, but these use only topical agents (Akesson et al., 2019).

The use of oral antibiotics in decolonization programs preoperatively has not been studied, however. It is known that they can reduce the carriage of *S.aureus* (Kumar et al., 2015), but they should be combined with topical agents in decolonization programs for MRSA as they do not reach sufficient nasal concentrations for effective decolonization (McConeghy et al., 2009; Simor et al., 2007). In addition, it is not known how long the potential decolonizing effect of oral antibiotics lasts. There is one study conducted among children colonized with *S.aureus* and with skin infections, where oral antibiotics reduced the carriage rate of *S.aureus* by half up to 50 days (Hogan et al., 2018).

On the other hand, there is for example a small randomized controlled trial by Sousa et al., where reducing *S.aureus* carriage rate with decolonization did not lead to a decreased incidence of PJI (Sousa et al., 2016). Hence it is also possible that the effect of preoperative oral antibiotics could be caused by some other mechanism. Perhaps the patients with preoperative antibiotic use had some unidentified active infections that were treated with the antibiotics. This seems unlikely, though, as the patients are rigorously screened preoperatively for possible infections.

Even if oral antibiotics could be used to reduce the PJI rate, for example through *S.aureus* decolonization, their widespread use for this reason cannot be recommended. Firstly, in Study III the NNT value for preoperative oral antibiotics to prevent one PJI was high (211). Secondly, there are concerns for potential harms of indiscriminate use of antibiotics, such as the increased risk for *Clostridioides difficile* infection and an increase in the incidence of resistant bacteria. It has been shown that the use of non-MRSA antibiotics leads to increased rates of MRSA carriage (Cheng et al., 2008).

6.3.3 Late periprosthetic joint infections

There is an effort to prevent late hematogenous PJIs with different antimicrobial prophylaxis regimens before various surgical or dental procedures. The data to support recommendations on the prophylactic regimens is varied.

Study IV shows that the risk of developing a PJI as a result of bacteremia caused by gram-negative bacteria is very low. Still, the American Urological Association recommends antibiotic prophylaxis before certain genitourinary procedures for patients with recent (less than two years old) joint replacements or

immunocompromised patients (Wolf et al., 2008). Based on the results of Study IV, this recommendation probably leads to overuse of antibiotics, and should perhaps be modified.

Unfortunately, it was not possible to make any definite conclusions on the usefulness of antibiotic prophylaxis before dental procedures based on the results of Study IV. The study shows that bacteremias by viridans group streptococci lead to PJIs fairly often, even though the absolute numbers were low. It is known that these bacteria are mainly associated with dental or gastrointestinal sources (Aas et al., 2005; Shenep, 2000). However, the dental status or previous dental procedures of the study patients could not be evaluated nor the sources of bacteremias caused by viridans group streptococci, and thus no conclusions could be made on the risk for PJI after dental procedures.

The relatively high risk of developing a PJI as a consequence of bacteremia caused by beta-hemolytic streptococci and *S.aureus* reported in Study IV highlights the importance of good skin care in patients with joint replacements to prevent PJIs, as most of these bacteremias originate from the skin. In addition, good skin care is important in the prevention of erysipelas caused by beta-hemolytic streptococci, as contiguous spread from the infected skin to the joint replacement has been reported (Wouthuyzen-Bakker et al., 2018).

6.4 Strengths and weaknesses of the study

The biggest strengths of Studies II and III were the very large sample size and the availability of extensive register-based data on possible confounding factors. Even though the study setting was retrospective, the large sample size and prospective data collection compensate for this. In addition, there has been an estimation that the study population would have to be 50 000 patients in each study arm in order to reliably estimate the effect of screening and treating preoperative bacteriuria in a randomized controlled trial (Bouvet et al., 2014). In reality, this is not feasible and thus previous prospective studies on preoperative bacteriuria have been insufficiently powered (Cordero-Ampuero et al., 2013; Martinez-Velez et al., 2016; Ollivere et al., 2009; Sousa et al., 2014). In fact, Study II is the largest study conducted on the effect of preoperative bacteriuria on the risk for PJI to date (Gomez-Ochoa et al., 2019; Sousa et al., 2019).

Another major strength in Studies II and III was the use of data from the Social Insurance Institution of Finland. With the use of the national drug reimbursement

register, the chronic diseases of the study patients could be evaluated fairly reliably and extensively, despite the large patient population. However, the drug reimbursement criteria pose some limitations, as there are certain diseases (such as hypertension) where reimbursements are granted only to patients with more serious forms of the disease and so their prevalence in the study population could have been underestimated. Nevertheless, it is likely that these milder forms of the disease do not have an effect on the risk for PJI or bacteriuria, and thus the effect on the results was probably not significant. On the other hand, there are other diseases, such as chronic liver disease, where reimbursements for medications are not granted and thus their prevalence could not be evaluated. Yet, the fairly extensive evaluation of the effect of chronic diseases could also be used to rule out a so-called "healthy patient bias" in Study III, i.e. a situation where healthier patients are more likely to take care of themselves and thus more likely to seek medical attention, therefore perhaps receiving antibiotics more readily than others. This seems unlikely in the study population of Study III, as the patients with and without preoperative antibiotics were similar with respect to chronic diseases.

The use of preoperative antibiotics in general and in the treatment of bacteriuria could also be evaluated extensively using data from the prescription register of the Social Insurance Institution of Finland, as all antibiotic purchases in Finland are recorded in the register. However, due to the nature of the register, in-patient use of antibiotics could not be identified. Nevertheless, it can be assumed that this was negligible, as a serious infection requiring treatment in a hospital setting would have likely resulted in postponement of surgery. Information on indication for the antibiotics or who had prescribed them was also not available from the register data, nor were the dosages of the antibiotics. Thus, consumption rates in defined daily dosages could not be examined, but as the number of pills purchased was available, some calculations on consumption rates could be made.

The retrospective nature of the study imposed some limitations. This was seen for example in Study I where some of the parameters required for the different diagnostic criteria were not available for all patients (e.g. ESR or synovial fluid samples). Had it been possible to influence the diagnostic tests performed for the study patients, the results could have been different. Also, in Study II, the retrospective setting influenced some aspects of data collection: the timing of the urine samples could not be affected, even though most samples were collected close to the time of surgery. In addition, the urine sample was missing from 13% of the operations. However, this probably did not affect the results, as none of the PJIs in patients with no urine samples were caused by typical urinary tract pathogens and

the incidence of PJI was similar in patients with or without preoperative urine samples.

The lack of a gold standard for the diagnosis of a PJI also had an effect on the studies. In Study I, it was not possible to test the accuracy of either of the diagnostic criteria and thus it could not be used as a validation study for the new consensus meeting criteria. On the other hand, the PJI cases in Studies II and III were identified from prospectively collected infection surveillance data. Even though this type of data has been shown to be fairly reliable, it is known that some cases are inevitably missed (Huotari et al., 2010; Huotari et al., 2007b). To avoid this, multiple data sources were used in Studies I and IV, especially to identify late PJIs that are not found in routine PJI surveillance.

There were also other limitations with respect to data collection. It was not possible to differentiate between ASB and symptomatic UTI due to the lack of clinical data in Study II. In addition, information on preoperative creatinine levels or urinary tract diseases was not obtained. It is also possible that there is some yet unidentified confounding factor responsible for the association between preoperative oral antibiotic use and the decreased risk for PJI observed in Study III. Nevertheless, the effect of several known possible confounding factors was taken into account and the results were the same also in the propensity score-matched patient population. In Study IV, the sources of bacteremia could not be investigated. In addition, it was not possible to determine with absolute certainty whether all of the PJIs caused by bacteremias were truly so or vice versa, even though patient charts were reviewed to eliminate this error. Finally, as the study period in Study IV was limited (up to 12 years), some very late PJIs were inevitably missed, but it can be assumed that their numbers were fairly low and did not affect the results significantly.

6.5 Future considerations

Despite the attempts to formulate uniform diagnostic criteria for PJIs, there still remains the lack of a gold standard that could be used both in research and surveillance work, and applied perhaps to clinical work as well. There is a shift towards more objective criteria that is, in light of the results of Study I, probably a shift towards more comparable incidence numbers in benchmarking or research studies. More studies are needed to validate the proposed diagnostic criteria, however, as they are mainly based on expert opinion at the moment.

As the number of joint replacement surgeries is continually rising, the prevention of PJIs continues to be crucial as well. On the other hand, ineffective prevention methods should be discontinued, as they only lead to unnecessary costs and perhaps increased harm to the patients. Study II shows that screening for preoperative bacteriuria is not necessary in the prevention of PJIs and this has for example been discontinued in the Coxa Hospital leading to significant savings. The same policy should be adopted both nationally and internationally as well, especially to avoid unnecessary antibiotic prescriptions to patients. International recommendations to this effect have already been made (Ares et al., 2019), based partly on the results of Study II, but their implementation is still in process.

Other methods to prevent PJIs still require more research. The interesting finding of a decreased risk for PJI with preoperative oral antibiotic use in Study III needs further validation in a larger patient population. It is not yet known, whether any studies on the topic have been initiated, but hopefully more data will be available on the topic in the future.

Not only is the number of joint replacement surgeries performed on the rise, also the number of people living with replaced joints continues to increase as the population is getting older. Thus, more people are continually at risk of developing a late PJI as well, making prevention of late hematogenous PJIs of high importance as well. Unfortunately, no specific patient-related risk factors for the development of hematogenous PJIs could be identified in Study IV, but perhaps in the future more efforts should be focused on the prevention of bacteremias caused by pathogens that are associated with a high risk of developing a hematogenous PJI, such as *S.aureus* and beta-hemolytic streptococci.

7 SUMMARY AND CONCLUSIONS

The main findings of this study are summarized as follows:

1) Fewer patients fulfil the new, more objective diagnostic criteria for PJI than the old criteria. A large proportion of the cases where the diagnosis was based solely on the opinion of the treating clinician failed to meet the new criteria. It is crucial to take into account the differences between the diagnostic criteria used when benchmarking or examining the results of surveillance or clinical studies.
2) Preoperative bacteriuria is not associated with an increased risk for PJI and therefore urine screening should not be performed preoperatively on asymptomatic patients before elective joint replacement surgery. Furthermore, treating preoperative bacteriuria does not have an effect on the risk for PJI. Thus, asymptomatic patients with preoperative bacteriuria should not be treated with antibiotics.
3) The use of oral antibiotics before joint replacement surgery is more common than in the general population. It is associated with a decreased risk for PJI, possibly due to a reduced rate of *S.aureus* carriage, but the significance of this novel result is yet to be determined. At the moment, indiscriminate use of oral antibiotics before joint replacement surgery cannot be recommended, even though active infections should be treated in order to prevent subsequent SSIs.
4) The development of a PJI as a consequence of bacteremia is mostly dependent on the pathogen causing the bacteremia. The risk is the highest for *S.aureus* and beta-hemolytic streptococci, but very low for gram-negative bacteria and coagulase-negative staphylococci. Repeated episodes of bacteremia increase the risk for developing a PJI during bacteremia, but no other patient-related risk factors could be found. The risk for the development of a PJI is the highest for bacteremias occurring within one year from previous surgery. Thus, when evaluating the risk of PJI in a patient with bacteremia, the pathogen, timing of the infection with respect to previous surgery and the history of the patient should be taken into account.

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PUBLICATIONS

PUBLICATION I

Concordance between the old and new diagnostic criteria for periprosthetic joint infection

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ORIGINAL PAPER

Concordance between the old and new diagnostic criteria for periprosthetic joint infection

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Abstract
Purpose There is no uniform definition for periprosthetic joint infection (PJI). New diagnostic criteria were formulated in an international consensus meeting in 2013 and adopted by Centers for Disease Control (CDC) in 2016. The purpose of this study is to compare the new diagnostic criteria with the old CDC criteria from the year 1992.
Methods Patients, who had been treated for PJI of hip or knee from 2002 to 2014, in a tertiary care hospital, were identified. Patient records were reviewed by a physician to identify PJI cases fulfilling the old or new CDC criteria and to record data concerning the diagnostic criteria. PJI frequencies were calculated for the two diagnostic criteria sets. Cross tables were formed to compare the concordance between the two sets of criteria in the whole material and in different clinical subgroups.
Results Overall 405 cases fulfilling either or both sets of criteria for PJI were identified. 73 (18%) of the patients fulfilled only the old criteria, whereas only one (0.2%) fulfilled only the new criteria. Of the patients who did not fulfil the new criteria, in 39 (53%) the diagnosis was based solely on the clinician's opinion.
Conclusions The number of PJIs is notably lower when using the new, more objective, diagnostic criteria. A large portion of the cases diagnosed as infection by the treating clinician, did not fulfil the new diagnostic criteria.

Keywords Prosthetic joint infection · Healthcare-associated infections · Surveillance · Diagnosis

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Introduction

Due to the considerable morbidity and high costs of periprosthetic joint infections (PJIs), they are part of most surgical site infection surveillance programs [1], and indeed surveillance seems to reduce infection incidence and it is cost-effective [2–4]. However, there has been no uniform definition of PJI in clinical studies and several diagnostic criteria have been used both in clinical work and in epidemiological studies [5–8]. On the other hand, the definition of PJI is dependent on the purpose of use, e.g., whether it is used for surveillance, clinical diagnosis making, or clinical research.

To receive reliable epidemiological data, it is crucial that the definition of surgical site infections is uniform in the organizations participating in the surveillance. In surgical site infection surveillance programs, PJIs have been identified according to the Centers for Disease Control and Prevention (CDC) criteria from the year 1992 (Table 1) [9]. Due to the variability in the diagnostic criteria of PJI, there has been an international attempt to formulate a set of diagnostic criteria that could be widely adopted [10]. In 2013, an international consensus meeting on PJI produced a new set of diagnostic criteria (Table 1) [11], which were adapted from the criteria originally suggested by the Musculoskeletal Infection Society in 2011 [10], and which have been later adopted by CDC [12]. The new criteria are more

Table 1 The old CDC and the new consensus meeting criteria for prosthetic joint infection [9, 11]

Definition of PJI according to the 1992 CDC criteria	Definition of PJI proposed by the consensus meeting 2013
Infection involves any part of the anatomy (e.g., organs or spaces), other than the incision, which was opened or manipulated during an operation AND patient has at least one of the following:	Two positive periprosthetic cultures with phenotypically identical organisms OR a sinus tract communicating with the joint OR having three of the following minor criteria:
Purulent drainage from a drain that is placed through a stab wound into the organ/space	Elevated serum C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR)[a]
Organisms isolated from an aseptically obtained culture of fluid or tissue in the organ/space	Elevated synovial fluid white blood cell (WBC) count or change on leucocyte esterase test strip[b]
An abscess or other evidence of infection involving the organ/space that is found on direct examination, during reoperation, or by histopathologic or radiologic examination	Elevated synovial fluid polymorphonuclear neutrophil percentage (PMN%)[c]
	Positive histological analysis of periprosthetic tissue
Diagnosis of an organ/space SSI by a surgeon or attending physician	A single positive culture

[a] Cut-off values for CRP >100 for early infections (less than 6 weeks from previous operation) and >10 for delayed/late infections (over 6 weeks from previous operation), cut-off value for ESR >30 (delayed/late infections, ESR does not apply for early infections)

[b] Cut-off value for synovial fluid WBC count >10,000 for early infections and >3000 for delayed/late infections

[c] Cut-off value for PMN% >90% for early infections and >80% for delayed/late infections

detailed and are based more on laboratory testing. In addition, a diagnosis of PJI by the treating clinician alone is no longer considered sufficient to make the diagnosis.

The purpose of this study was to compare the old CDC criteria for diagnosing PJI with the new consensus meeting criteria from 2013 in patients with suspected PJI. Furthermore, the reasons for potential discordance between the two criteria were investigated.

Methods

This is a retrospective study of patients treated for PJI of hip or knee from September 2002 until December 2014 in the Coxa Hospital for Joint Replacement, Tampere, Finland. The hospital is a public funded tertiary hospital and is responsible for providing prosthetic joint surgery within the Pirkanmaa Hospital District (population-base ca. 500,000 inhabitants). It is also the referral centre for complications involving prosthetic joints. Approximately 3000 arthroplasties are performed there annually. All included patients had a previous hip or knee arthroplasty operation in 2013 or earlier (with no time limit, in Coxa or in other hospitals) to have at least a 1-year follow-up period for the operated joints.

To identify all possible PJIs from the study period, data were gathered from six different sources: (1) prospective surveillance data following the National Nosocomial Infections Surveillance standards gathered in the national Finnish Hospital Infection Program (SIRO) (2005–2010, 2012–2013) of the National Institute of Health and Welfare [13, 14], (2) cases identified by active post-discharge surveillance conducted by infection control nurse according to the old CDC criteria (2002–2014), (3) positive bacterial cultures of joint aspirates or tissue cultures from samples taken in the Coxa hospital, identified from the electronic records of the microbiological laboratory, which is an accredited laboratory of the Tampere University Hospital (2002–2014), (4) all patients with a prosthetic joint operation done because of an infection (ICD-10 diagnosis code T84.5 or T81.4) that had been recorded in the hospital discharge records (2002–2014), (5) all revision arthroplasties performed because of an infection and recorded in the local hospital database, where operative data are gathered prospectively (2002–2014), and (6) cases recorded in the hospital's own infection register, which was created for clinical purposes and for collecting data on the quality of care (2012–2014).

Patient records of all possible infection cases identified from the above-mentioned six sources were thoroughly reviewed by one of the authors (M.H.), a specialist registrar in infectious diseases, to identify PJI cases fulfilling the old or new criteria and to record data concerning the diagnostic criteria to compare them. Cases that were difficult to define ($n = 67$) were reviewed also by two infectious diseases specialists (J.S., M.K.). Cases were excluded from the study: (1) if the infection was classified as a superficial or deep wound infection, (2) if the infected prosthesis was a hemi endoprosthesis implanted for the treatment of hip fracture, (3) if the infection was related to osteosynthesis material, temporary spacer or native joint or to a joint other than knee or hip, or (4) if the case was not an infection at all (e.g., a positive bacterial culture, which had been deemed to be a contamination and left untreated, or if the recorded procedure was done for some other reason, but mistakenly recorded as an infection) (Fig. 1).

For each identified PJI case, it was determined separately if the case fulfilled the old [9] or the new [11] diagnostic criteria. The date of the occurrence of infection was determined to be either the day when the new criteria

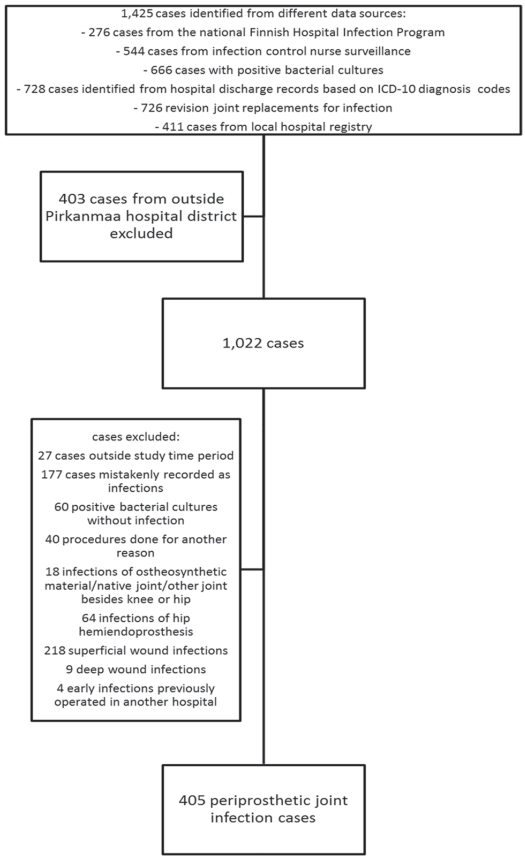

Fig. 1 The number of suspected PJI cases identified from different data sources and the number of cases excluded from the study

were met or, if that did not occur, the day when treatment was started (i.e., usually the day of revision arthroplasty). The PJIs were classified as early, if they occurred within 3 months after the previous operation, delayed, if they occurred within 3–12 months and late, if they occurred after 1 year [7, 15]. Cut-off values for different laboratory tests were determined according the consensus meeting suggestions [11].

Statistical methods

Frequencies were calculated and cross tables were formed to compare the concordance between the two sets of criteria in the whole material and in different clinical subgroups. Cases, which fulfilled only the old CDC criteria and where the diagnosis was based on the clinician's opinion alone, and culture negative cases, were examined separately.

All data analyses and management were performed using SPSS for Windows 23.0 statistical software package.

Results

Overall 405 cases fulfilling either or both sets of criteria for PJI were identified. 73 out of 405 cases (18%) met only the old CDC criteria, but not the new consensus meeting criteria, whereas only one (0.2%) of the cases fulfilled only the new criteria (Table 2).

The distribution of cases fulfilling either or both diagnostic criteria sets according to clinical subgroups is shown in Table 2. The distribution of cases was similar when analysed separately for hip prostheses, knee prostheses, primary and revision arthroplasties, according to gender, age and different infection types. As positive bacterial culture belongs to both diagnostic criteria, most culture positive patients fulfilled both sets. The number of cases that met each specific diagnostic criterion in the old and new criteria sets is shown in Table 3.

Possible sources of discordance between the diagnostic criteria sets were investigated, including the clinician's diagnosis, lack of ESR measurement and culture negative cases. Of the patients who did not fulfil the new criteria, in 39 (10% of the whole study population) the diagnosis was based solely on the clinician's opinion. Of these patients, 16 (41%) had an increased number of leucocytes in the joint aspirate and 16 (41%) an increased number of polymorphonuclear cells. Thirteen (33%) of these patients had an elevated CRP and ESR value, and 30 (77%) had an increased CRP value. Fifteen (39%) fulfilled two of the minor criteria from the new consensus meeting criteria set. If patients, who fulfilled only two minor criteria, were also considered to have PJI, 33 additional patients would fulfil the new consensus meeting criteria, leading to a total of 365 PJI cases identified by the new criteria.

ESR was measured in 152 (38%) cases in the whole patient population. There was only one delayed/late infection with an increased ESR value, but with normal CRP. If patients with a delayed or late infection and with an elevated CRP value, but whose ESR was not measured, were assumed to have an increased ESR, 169 patients would fulfil three or more minor criteria of the new consensus meeting criteria. 17 new infectious cases would be identified in total, as most of these patients also fulfilled either one of the main criteria. Of these new cases, 13 cases did not meet any of the old CDC criteria, besides the clinician's diagnosis. If they were considered to fulfil the new criteria, there are still 26 (6%) cases in the whole study population, who did not meet any other diagnostic criteria besides the clinician's opinion.

Table 2 Number of cases fulfilling the different diagnostic criteria sets in different subgroups

	Cases	Cases fulfilling only the old CDC criteria	Cases fulfilling only the new consensus meeting criteria	Cases fulfilling both sets of criteria
	n	*n* (%)	*n* (%)	*n* (%)
All cases	405	73 (18)	1 (0.2)	331 (82)
Joints				
Hips	167	32 (19)	1 (0.6)	134 (80)
Knees	238	41 (17)	0	197 (83)
Previous operation				
Primary arthroplasty	285	48 (17)	1 (0.4)	236 (83)
Revision arthroplasty	120	25 (21)	0	95 (79)
Gender				
Men	177	28 (16)	0	49 (84)
Women	228	45 (20)	1 (0.4)	182 (80)
Age				
≤70	195	37 (19)	0	158 (81)
>70	210	36 (17)	1 (0.5)	173 (82)
Bacterial culture				
Positive	327	28 (9)	0	299 (91)
Negative	78	45 (58)	1 (1.3)	32 (41)
Infection type				
Early	151	24(16)	1 (0.7)	126 (83)
Delayed	63	15 (24)	0	48 (76)
Late	191	34 (18)	0	157 (82)
Infections diagnosed in				
2002–2006	97	29 (30)	0	68 (70)
2007–2010	165	20 (12)	0	145 (88)
2011–2014	143	24 (17)	1 (0.7)	118 (83)

There were six cases of late haematogenous infections, where CRP was elevated, but ESR remained within normal range. All had positive blood cultures.

Of culture negative patients, 45/78 (58%) did not meet the new consensus meeting criteria for PJI (Table 2). However, 38 culture negative patients (49%) fulfilled two minor criteria from the new criteria set. 38 (49%) had an increased number of leucocytes and 37 (47%) an increased number of polymorphonuclear cells in the joint aspirate. CRP and ESR were elevated in 38 (49%) of the patients and CRP was elevated in 58 (74%). Despite an increase over time in the number of intraoperative tissue samples taken, the proportion of culture positive cases did not increase over time. 49 (63%) of the culture negative cases had four or more samples taken.

Discussion

This study indicates notable discordance between the old CDC criteria and the new consensus meeting criteria for PJI: one fifth of the cases were identified as PJIs only by the old criteria, but not by the new ones. This was mainly because a large portion of the cases diagnosed as PJI by the treating clinician did not fulfil the new diagnostic criteria. The discordance leads to different numbers of infected cases and the incidence of PJI is lower when using the new, more objective, diagnostic criteria.

The old and new criteria for PJI have not been compared before, and there has not been a study to validate the new set of diagnostic criteria. The new criteria were formed as an attempt to formulate a gold standard for the diagnosis of PJI. This study raises the question whether true PJI cases could be missed by the new criteria as such a large number of patients previously diagnosed as having a PJI did not fulfil them. On the other hand, it is likely that some of the patients diagnosed as having a PJI according to the old criteria, were in fact not infected. This is especially relevant when considering surveillance records and their accuracy. For example, if the resources for clinical diagnosis of PJI in a hospital are not sufficient, there is a possibility that surveillance criteria that are too strict will fail to recognize PJIs.

Table 3 Number of cases fulfilling the different diagnostic criteria

	Number	% of all cases
Old CDC criteria		
Total	404	100
Purulent drainage from a drain	0	0
Organisms are identified from an aseptically obtained fluid or tissue in the space by a culture	327	81
An abscess or other evidence of infection involving the organ/space that is detected on gross anatomical or histopathologic exam, or imaging test	38	9
Diagnosis of a PJI by a surgeon or attending physician	400	99
New consensus meeting criteria		
Total	332	82
Two positive periprosthetic cultures with phenotypically identical organisms	239	59
A sinus tract communicating with the joint	82	20
Having three of the following minor criteria	106	26
Elevated serum C-reactive protein (CRP) AND erythrocyte sedimentation rate (ESR)[a]	199	49
Elevated synovial fluid white blood cell count[b]	192	47
Elevated synovial fluid polymorphonuclear neutrophil percentage (PMN%)[c]	178	44
Positive histological analysis of periprosthetic tissue	11	3
A single positive culture	88	22

[a] CRP was measured from 402 patients, ESR from 152 patients and both from 152 patients. Early infections with an elevated CRP were considered to be fulfilling this criterion

[b] Synovial fluid WBC was measured from 209 patients

[c] Synovial fluid PMN% was measured from 198 patients

It is notable that in 10% of the cases the diagnosis was based solely on the clinician's opinion and no other diagnostic criteria were fulfilled. It is possible that at least some of these cases are still true PJIs. Firstly, they did not fulfil three minor criteria of the new consensus meeting criteria, because ESR was not measured in many of these cases, as CRP is the preferred inflammatory marker used. The value of measuring both ESR and CRP as markers of PJI has been questioned. For example, Johnson et al. [16] showed that CRP alone and CRP and ESR in combination had the same sensitivity when diagnosing PJI of the knee, but the number of false negative cases increased from 5.3 to 11.1% when they were used in combination. Additionally, Ghanem et al. [17] showed that using both CRP and ESR in combination resulted in lower sensitivity than using either one as a marker of PJI. There have also been reports of PJIs with normal CRP and ESR values [18]. Therefore, it is probably unnecessary to require both ESR and CRP for the diagnosis of PJI. Secondly, the cut-off values for leucocytes and polymorphonuclear cells are based on a small number of studies with large variation [11]. High sensitivity and specificity for cut-off values lower than those in the new criteria, ranging from 1100 to 3450 for WBC and 64 to 78% for PMN%, have been reported [19–22]. If lower cut-off values had been used in this study, it is probable that more patients would have been identified as having PJI according to the new criteria.

On the other hand it is possible that some of the cases diagnosed as infections based on the clinician's diagnosis may have represented reactions to metal debris from metal-on-metal hip prostheses [23–25]. Before this phenomenon was recognized, such cases may have been mistakenly diagnosed as PJIs. Unfortunately the types of prosthetic joints in this study population were not recorded, so the possible number of metal-on-metal reactions falsely diagnosed as infections could not be evaluated.

A positive bacterial culture was important in the diagnosis of PJI in this material (Table 3). About 80% of patients had a positive bacterial culture, and 59% had at least two positive cultures, which was the most commonly met of part of the new consensus meeting criteria. Bacterial cultures have had a well-established role in the diagnosis of PJI, even though there has been some debate about the number of positive samples required to make a definitive diagnosis. Some studies have shown that fewer than four samples obtained may decrease the sensitivity of the intraoperative bacterial cultures [26, 27]. Nonetheless in this study almost two-thirds of the culture negative cases had four or more samples taken.

Almost two-thirds of the culture negative patients fulfilled only the old CDC criteria, which again reflect the importance of a positive bacterial culture in the new consensus meeting criteria. Nevertheless, there is a possibility that some true, but culture negative prosthetic joint infections were missed by the new criteria; almost half of

the culture negative patients fulfilled two other minor criteria, and thus if they had had a single positive bacterial culture, they would have been diagnosed as having a PJI also by the new criteria. A history of antibiotic use before the diagnosis of infection could explain the negative bacterial cultures [28, 29], but this information could not be recorded in this study.

There are some limitations in this study. Firstly, some of the parameters, such as ESR or synovial fluid samples, required by the different diagnostic criteria were not measured from all patients. Thus, it is possible that some patients could have fulfilled the new diagnostic criteria had these parameters been examined, making the two criteria more concordant. Since this was a retrospective study, it was not possible to influence which diagnostic tests were performed for each patient. Secondly, there is still no gold standard for diagnosing PJIs, so there was no method of testing the accuracy of either of the diagnostic criteria. For example, there is a possibility that the new criteria are not sufficient to identify all the infectious cases, especially those caused by low virulence organisms, as was suggested by Kapadia et al. [15] in a recent review. Thirdly, due to the large number of prosthetic joint operations in the study period, it was not possible to gather information regarding the different diagnostic criteria from the whole population, but only from those identified as infected by the different data sources. Thus, Cohen's kappa estimate could not be used to compare the different criteria. However, as the main purpose of this study was to compare cases identified as infected by the different criteria and their differences, this was not deemed necessary. Finally, it is acknowledged that surgical site infection surveillance programs using the CDC definitions are limited to 90-day post-operative follow-up [12] whereas this study included patients who had been operated several years before. However, when comparing the different infection subgroups (early, delayed and late infections), the number of patients identified by the two sets of criteria were similar, suggesting that the same criteria can also be used for the diagnosis of late PJIs.

In conclusion, fewer patients fulfil the new consensus meeting criteria for PJI than the old CDC criteria. A large portion of the cases diagnosed as PJI by the treating clinician, did not fulfil the new diagnostic criteria. The two sets of diagnostic criteria examined in this study reflect a shift from a diagnosis relying only on the treating clinician's opinion to a diagnosis based on objective measurements. In clinical work the diagnosis made by the treating clinician is important, but there is a need for uniform and objective diagnostic criteria for PJI in surveillance and benchmarking. It is important to be aware of the differences between the diagnostic criteria when benchmarking or comparing the results of surveillance studies.

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Compliance with ethical standards

Ethical standards According to the Finnish national legislation, patient consent or approval by the ethics committee is not required in retrospective studies like this, and thus none was acquired.

Conflict of interest The authors declare that they have no conflicts of interest.

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PUBLICATION II

The impact of preoperative bacteriuria on the risk of periprosthetic joint infection after primary knee or hip replacement: a retrospective study with a 1-year follow up

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Original article

The impact of preoperative bacteriuria on the risk of periprosthetic joint infection after primary knee or hip replacement: a retrospective study with a 1-year follow up

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ABSTRACT

Objectives: Patients who undergo elective joint replacement are traditionally screened and treated for preoperative bacteriuria to prevent periprosthetic joint infection (PJI). More recently, this practice has been questioned. The purpose of this study was to determine whether preoperative bacteriuria is associated with an increased risk of PJI.

Methods: Patients who had undergone a primary hip or knee replacement in a tertiary care hospital between September 2002 and December 2013 were identified from the hospital database (23 171 joint replacements, 10 200 hips, and 12 971 knees). The results of urine cultures taken within 90 days before the operation were obtained. Patients with subsequent PJI or superficial wound infection in a 1-year follow-up period were identified based on prospective infection surveillance. The association between bacteriuria and PJI was examined using a multivariable logistic regression model that included information on the operated joint, age, gender and the patients' chronic diseases.

Results: The incidence of PJI was 0.68% ($n = 158$). Preoperative bacteriuria was not associated with an increased risk of PJI either in the univariate (0.51% versus 0.71%, OR 0.72, 95% CI 0.34–1.54) or in the multivariable (OR 0.82, 95% CI 0.38–1.77) analysis. There were no cases where PJI was caused by a pathogen identified in the preoperative urine culture. Results were similar for superficial infections.

Conclusions: There was no association between preoperative bacteriuria and postoperative surgical site infection. Based on these results, it seems that the preoperative screening and treatment of asymptomatic bacteriuria is not required. **M. Honkanen, Clin Microbiol Infect 2018;24:376**

Introduction

To prevent postoperative infections, patients undergoing elective joint replacement have traditionally been routinely screened for bacteriuria [1,2]. The risk for haematogenous seeding to a prosthetic joint from a postoperative urinary tract infection has been reported [3–5]. However, the association between preoperative asymptomatic bacteriuria (ASB) and periprosthetic joint infection (PJI) is less clear. Therefore, the efficacy of the practice of routine urine cultures has been questioned in recent studies [6,7].

The relationship between preoperative ASB and PJI has previously been examined in small retrospective studies [8,9] and in one large registry-based study [10]. However, only in the last decade have there been prospective studies carried out on the subject [7,11–15]. Some of these studies have shown an increased risk of postoperative infection complications in patients with preoperative ASB [11,14], but direct seeding to the prosthetic joint has not been reported. Furthermore, treating preoperative ASB with antibiotics has not been shown to be effective in preventing PJI [7,12,14,15].

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ASB is fairly common in the general population, especially in older women. In people in their 70s, the estimated prevalence of ASB is between 11% and 16% for women and between 4% and 19% for men [16]. For women and men aged ≥ 80 years, the estimated prevalence is 20% and 10%, respectively [17]. In patients undergoing elective joint replacement, the prevalence of ASB varies from 3.5% to 36% [8,12–15]. The unnecessary treatment of ASB with antibiotics has several drawbacks, such as the emergence of resistant bacterial strains, the occurrence of *Clostridium difficile* infection, and increased costs [18,19], and is therefore not currently recommended for the general population [16].

Guidelines concerning the screening of the preoperative urine samples of asymptomatic patients undergoing elective joint replacement surgery are conflicting. The British Orthopaedic Association recommends preoperative urine screening [6], whereas the consensus statement from the International Consensus Meeting on Periprosthetic Joint Infection opposes it [20]. The current Infectious Diseases Society of America guideline gives no recommendations on the matter [16], but lists urine screening before joint replacement surgery as an important topic for future research as does the International Consensus statement [20].

The purpose of this retrospective observational study with a 1-year follow up was therefore to determine whether preoperative bacteriuria before elective joint replacement increases the risk of PJI or surgical site infection in a 1-year follow up.

Materials and methods

This retrospective study was performed at the Coxa Hospital for Joint Replacement, Tampere, Finland, a publicly funded tertiary orthopaedic hospital. Patients who had undergone primary hip or knee replacement between September 2002 and December 2013 were identified from the local prospective joint replacement database. According to the national legislation, patient consent is not required in retrospective studies like this. If more than one primary joint replacement was performed on a patient during the study period, each joint replacement was considered separately. With a few exceptions, the patients underwent surgery under spinal anaesthesia. Unless contraindicated, a single dose of cefuroxime was used as antibiotic prophylaxis. Cemented prostheses were fixed with gentamicin-impregnated bone cement.

Urine cultures were part of the routine preoperative laboratory testing for all patients. For this study, the results of urine cultures taken within 90 days before the joint replacement were obtained from the electronic records of a microbiology laboratory accredited by Tampere University Hospital. The species of bacteria found in the urine samples and their antibiotic susceptibility data were recorded. If more than one urine sample was taken, the one taken closest to the date of operation was used in the analyses. All bacterial growth in the urine was considered significant. If more than one bacterium was reported in the sample, they were all recorded. The outcomes with patients with missing urine samples are reported separately.

Information regarding chronic diseases was gathered from the drug reimbursement register of the Social Insurance Institution of Finland. All permanent residents of Finland are covered by national health insurance, which includes drug reimbursements. To receive reimbursements, patients require a certificate issued by the treating doctor and the right to reimbursement is granted based on the specific diagnostic criteria for each disease. Patients with a valid entitlement to reimbursement for certain chronic diseases (diabetes, rheumatic diseases, hypertension, chronic heart failure, chronic coronary disease, arrhythmias, chronic lung disease, Parkinson's disease, epilepsy, Alzheimer's disease, psychotic disorders, haematological and solid malignancies) at the time of the joint replacement were identified. For the analyses, chronic heart failure, chronic coronary disease and arrhythmias were grouped together, as were Parkinson's disease, epilepsy, Alzheimer's disease and psychotic disorders.

Information on the antibiotics (identified based on their ATC codes) purchased by the patients within 90 days before the joint replacement was gathered from the prescription register of the Social Insurance Institution of Finland. In Finland, antibiotics are not available without a prescription and all purchases are recorded in the national prescription register. The type of antibiotic and the date of purchase were also recorded. Antibiotics for preoperative bacteriuria were prescribed by orthopaedists at the operating hospital, but other antibiotics could have been prescribed elsewhere.

Cases of infection were identified from prospective post-discharge surveillance data gathered by an infection control nurse according to the Centers for Disease Control and Prevention criteria [21] and National Nosocomial Infection Surveillance system methodology adapted for Finland [22]. The primary outcome was the occurrence of PJI. The occurrence of any surgical site infection (superficial or deep incisional infection or PJI) was analysed as a secondary outcome. Microbiological data on the occurrence of PJI were collected from the electronic records of the microbiology laboratory. In order to have a 1-year follow-up period for all operated joints, cases of infection recorded between September 2002 and December 2014 were identified.

Statistical analysis

All data analyses and management were performed using the SPSS for Windows 23.0 statistical software package.

Categorical variables were compared with χ^2 test and continuous variables (age) with Student's independent-samples *t*-test. A p value <0.05 was considered statistically significant.

The association between potential risk factors for infection and the outcome (PJIs and all infections separately) was examined using logistic regression with univariate analysis. A multivariable model was developed that included all potential risk factors for infection that were examined in the univariate analysis.

Results

In total, 23 171 primary joint replacements were performed in 17 562 people between September 2002 and December 2013. Of these, 10 200 (44%) were primary hip and 12 971 (56%) primary knee replacements, respectively. In addition, 1805 (8%) operations

Table 1
Bacteria found in the preoperative urine samples (some samples contained more than one bacterium, these are recorded separately)

Bacterium species	*n* (*N*=1378)	%
Gram-negative		
Escherichia coli	822	59.7
Klebsiella	114	8.3
Proteus	36	2.6
Citrobacter	10	0.7
Morganella	4	0.3
Pseudomonas	23	1.7
Acinetobacter	8	0.6
Other	39	2.8
Gram-positive		
Coagulase-negative staphylococci	63	4.6
Staphylococcus aureus	11	0.8
Streptococcus agalactiae	136	9.9
Enterococcus spp.	149	10.8
Other	8	0.6

were simultaneous bilateral hip or knee replacements. From the total number of operations, 14 361 (62%) were performed for women and 8810 (38%) for men. The mean age at the time of operation was 67 years (range 14 years to 109 years).

A preoperative urine sample was available in 20 226 operations (87%), and 1378 (6.8%) of the urine cultures were positive. Most of the samples were collected within 30 days before the surgery (see Supplementary material, Fig. S1). The bacteria found in the urine are listed in Table 1. Of the positive urine samples, 1237 (90%) were in women. Patients with positive urine cultures were also older and had more chronic diseases than patients with a negative urine culture (see Supplementary material, Table S1). Positive urine cultures were more frequent in patients undergoing knee replacement than hip replacement. A preoperative urine sample was missing in 2945 (12.7%) operations. There were more missing samples in men than in women (16% versus 11%) and more before hip replacements than before knee replacements (16% versus 10%). The mean age of the patients with a missing urine sample was also lower (64 years versus 68 years) and there were fewer patients suffering from diabetes (7.1% versus 8.2%).

During the 1-year follow up, 490 surgical site infections (2.11% of the study population) were identified. Of these, 158 were PJIs, giving an incidence of 0.68% in the whole study population. The incidence of PJI was 0.57% (58/10 200) for hip replacements and 0.77% (100/12 971) for knee replacements. In seven (4%) of the PJI cases, the preoperative urine culture was positive, and in 133 (84%) cases the culture was negative. In 18 (11%) PJI cases, the urine sample was missing. In the PJI cases with a positive urine culture, the pathogens found in the urine cultures and those identified from the joint were not the same in any of the cases (Table 2). Furthermore, no evidence to link preoperative urine cultures to superficial or deep wound infections could be found (data not shown).

In patients with a positive urine culture, the incidence of PJI was 0.51% (7/1378), and 0.71% (133/18 848) in patients with a negative culture. The incidence of all surgical site infections was 1.89% (26/1378) in patients with a positive urine culture and 2.18% (411/18 848) in those patients with a negative urine culture. No statistically significant association was found in univariate or multivariable analysis between positive urine culture and PJI or all surgical site infections (Table 3). The impact of other risk factors on the risk of PJI is presented in Table 3.

Of the patients with preoperative bacteriuria, 344 (25%) received antibiotics after the urine sample was taken. In 51 patients, the prescribed antibiotic was not effective against the pathogen found in the urine, mostly because of the acquired or natural resistance properties of the pathogen. Of the 293 patients with effective antibiotic treatment, one (0.34%) had a subsequent PJI, whereas of the 1085 patients with bacteriuria and no or no effective antibiotics, six (0.55%) had a PJI. Treating the bacteriuria with effective antibiotics did not affect the risk of PJI (OR 0.62, 95% CI 0.07–5.14).

There were 18 PJI cases (incidence 0.61%) and 35 superficial or deep wound infections (incidence 1.19%) among the 2945 patients without preoperative urine samples. These incidences were similar to the overall incidence. In 11 PJI cases, the pathogens causing the infection could be identified (*Staphylococcus aureus*, *Corynebacterium* species and coagulase-negative staphylococci) and none were typical urinary tract pathogens.

Discussion

The findings of this large retrospective study show that there is no association between preoperative bacteriuria and subsequent postoperative PJI after primary joint replacement when possible confounding factors, such as chronic diseases, are taken into account. Furthermore, there were no postoperative infections caused by the pathogens found in the preoperative urine samples and treating the bacteriuria with effective antibiotics did not decrease the incidence of PJI.

During the study, the influence of possible confounding factors, especially chronic diseases, was taken into account extensively. Furthermore, the data were based on prospective systematic surveillance, which strengthens the reliability of this retrospective study. It has been estimated that to conduct a reliable prospective randomized controlled trial that compares the screening and treatment of bacteriuria with no screening and treatment, it would require a study population of 50 000 patients in each study arm, which is not feasible [13]. Previous prospective studies [11,12,14,15] have had small sample sizes, and so have been insufficiently powered.

The incidence of PJI in this study (0.68%; 0.57% for hip and 0.77% for knee replacements) is similar to the findings of previous studies: 0.3%–0.6% for hip replacements [23,24] and 0.8%–1.1% for knee replacements [23–25], with the exception of a study by Lamb *et al.* [7], where the overall incidence of PJI was very low (0.02%). The cases of infection in the present study were identified by postoperative infection surveillance that has been shown to miss some infections [22]. This should not, however, be seen to bias the findings of this study. Male gender, age, knee replacement and diabetes were all associated with an increased risk of PJI, which is in line with previous studies [25,26]. Obesity has also been shown to be a risk factor for PJI [26]; however, body mass index data were not available for this study population.

The prevalence of preoperative bacteriuria was 6.8%, which is similar to two earlier Spanish studies [12,15] and slightly lower than in other studies [8,13,14]. There was no association between preoperative bacteriuria and postoperative surgical site infection or PJI. Furthermore, in the cases with preoperative bacteriuria and

Table 2
Comparison between pathogens found in the preoperative urine sample and postoperative prosthetic joint infection (PJI)

Case number	Age	Gender	Operated joint	Time between urine sample and surgery (days)	Time between surgery and infection (days)	Pathogen found in urine	Pathogen causing PJI
1	81	Female	Hip	36	16	*Enterococcus faecalis*	*Staphylococcus aureus*
2	76	Female	Knee	9	16	*Escherichia coli*	NA[a]
3	76	Male	Knee	31	18	*Enterococcus faecalis*	Coagulase-negative staphylococcus
4	63	Female	Knee	11	36	*Klebsiella pneumoniae*	*Staphylococcus aureus*
5	81	Female	Knee	64	85	*Escherichia coli*	Coagulase-negative staphylococcus
6	75	Female	Knee	0	142	*Escherichia coli*	NA[a]
7	79	Male	Knee	29	258	Coagulase-negative staphylococcus	*Staphylococcus epidermidis*[b]

[a] Culture-negative PJI.
[b] Different antibiotic resistance pattern from the strain found in the urine.

Table 3
Potential factors affecting the risk of periprosthetic joint infection and any surgical site infection in primary joint replacements

Factor	Periprosthetic joint infection				Any surgical site infection			
	Univariate analysis		Multivariable analysis[a]		Univariate analysis		Multivariable analysis[a]	
	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
Positive urine culture	0.72	0.34–1.54	0.82	0.38–1.77	0.86	0.58–1.29	0.92	0.61–1.39
Male gender	1.96	1.43–2.68	2.21	1.56–3.11	1.31	1.10–1.57	1.45	1.19–1.77
Knee replacement	1.36	0.98–1.88	1.43	1.01–2.04	1.53	1.27–1.85	1.58	1.29–1.94
Age	1.01	1.00–1.03	1.03	1.01–1.05	1.00	0.99–1.01	1.01	1.00–1.02
Chronic diseases								
Chronic heart disease[b]	0.78	0.55–1.10	0.58	0.28–1.21	0.97	0.80–1.17	0.73	0.48–1.12
Chronic lung disease	1.07	0.58–1.98	1.04	0.53–2.05	1.46	1.07–1.99	1.39	0.99–1.95
Diabetes	1.65	1.03–2.65	1.64	0.99–2.73	1.30	0.96–1.75	1.09	0.78–1.52
Hypertension	0.76	0.52–1.11	1.09	0.50–2.38	1.02	0.83–1.24	1.25	0.80–1.96
Malignancy	0.54	0.17–1.68	0.55	0.17–1.72	0.51	0.26–1.00	0.58	0.30–1.14
Neurological or psychiatric disorder[c]	1.02	0.45–2.30	1.15	0.51–2.63	1.04	0.65–1.65	1.21	0.76–1.92
Rheumatic disease	0.59	0.24–1.44	0.61	0.23–1.67	1.06	0.71–1.57	1.09	0.72–1.66

[a] All variables analysed in the univariate analysis were included in the multivariable analysis.
[b] Includes chronic heart failure, chronic coronary disease and arrhythmias.
[c] Includes Parkinson's disease, epilepsy, Alzheimer's disease and psychotic disorders.

subsequent PJI, the pathogens were not the same. In addition, treating the bacteriuria with antibiotics did not decrease the risk of PJI. Previous studies have yielded variable results. Several studies, such as the classic study by Glynn and Sheehan [8], have found no association between preoperative bacteriuria and PJI. However, the study by Glynn and Sheehan had a small sample size and a follow-up period of only 3 months. In a more recent study, Cordero-Ampuero *et al.* [12] found no association between preoperative bacteriuria and postoperative infection following hip replacement, and treating the bacteriuria with antibiotics had no effect on the incidence of infection. The same research group reported similar results for knee replacements [15]. Unlike earlier studies, the current study takes into account the effect of both chronic diseases and outpatient antibiotic use. Even so, the results are still in line with those of the above-mentioned studies.

On the other hand, Sousa *et al.* [14] found that patients with preoperative ASB had a statistically significantly increased risk of PJI, but the micro-organisms found in the urine and those causing the PJI were different. Furthermore, there was no difference in the incidence of PJI when comparing those patients who had received antibiotics for the bacteriuria and those who had not. This suggests that in patients with ASB there are some other factors that could contribute to the risk of PJI. In fact, the current study shows that patients with preoperative bacteriuria have more chronic diseases than patients with negative urine cultures.

There were some limitations in this study. First, this was a retrospective study, and therefore it was not possible to differentiate between asymptomatic bacteriuria and symptomatic urinary tract infection due to a lack of clinical data, and unfortunately the concentration of bacterial growth in the urine samples could not be retrieved from the laboratory data. Furthermore, the timing of urine samples taken before the operation could not be influenced. Most samples were, however, collected close to the surgery. Second, a urine sample was not available in 13% of the operations. However, none of the PJIs in patients with a missing urine sample were caused by pathogens that typically cause urinary tract infections. The incidence of PJI was not higher among patients with a missing urine sample than in the overall study population. Third, it was not possible to take into account all possible confounding factors. The drug reimbursement data gives a fairly accurate estimate of the prevalence of certain chronic diseases. However, due to the nature of the reimbursement criteria, in certain diseases (such as hypertension) patients who only have a mild form of the disease receive no reimbursements, and so their prevalence may be underestimated. These mild forms of diseases probably have less effect on the risk of bacteriuria and should therefore not affect the results. Furthermore, information on body mass index, serum creatinine level or urinary tract diseases could not be obtained.

This study adds to the growing body of evidence that supports the view that asymptomatic preoperative bacteriuria does not cause PJI, and hence it should not be screened or treated. This finding should be taken into account in future guidelines regarding the screening and treatment of preoperative ASB before joint replacement surgery.

Transparency declaration

Dr Honkanen reports grants from the Competitive State Research Financing of the Expert Responsibility area of Tampere University Hospital, during the conduct of the study. All authors report no other conflicts of interest.

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Authors' contribution

MH, EJ, MK, RH and JS designed the study and MH collected the data and wrote the first draft of the article. All authors participated in the interpretation of the data and revising the article. All authors have seen and approved the final version of the article.

Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.cmi.2017.07.022.

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PUBLICATION III

The effect of preoperative oral antibiotic use on the risk of periprosthetic joint infection after primary knee or hip replacement: a retrospective study with a 1-year follow-up

Honkanen M, Jämsen E, Karppelin M, Huttunen R, Syrjänen J.

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Original article

The effect of preoperative oral antibiotic use on the risk of periprosthetic joint infection after primary knee or hip replacement: a retrospective study with a 1-year follow-up

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ABSTRACT

Objectives: Antibiotics are used for various reasons before elective joint replacement surgery. The aim of this study was to investigate patients' use of oral antibiotics before joint replacement surgery and how this affects the risk for periprosthetic joint infection (PJI).

Methods: Patients having a primary hip or knee replacement in a tertiary care hospital between September 2002 and December 2013 were identified ($n = 23\,171$). Information on oral antibiotic courses purchased 90 days preoperatively and patients' chronic diseases was gathered. Patients with a PJI in a 1-year follow-up period were identified. The association between antibiotic use and PJI was examined using a multivariable logistic regression model and propensity score matching.

Results: One hundred and fifty-eight (0.68%) cases of PJI were identified. In total, 4106 (18%) joint replacement operations were preceded by at least one course of antibiotics. The incidence of PJI for patients with preoperative use of oral antibiotics was 0.29% (12/4106), whereas for patients without antibiotic use it was 0.77% (146/19 065). A preoperative antibiotic course was associated with a reduced risk for subsequent PJI in the multivariable model (OR 0.40, 95% CI 0.22–0.73). Similar results were found in the propensity score matched material (OR 0.34, 95% CI 0.18–0.65).

Conclusions: The use of oral antibiotics before elective joint replacement surgery is common and has a potential effect on the subsequent risk for PJI. Nevertheless, indiscriminate use of antibiotics before elective joint replacement surgery cannot be recommended, even though treatment of active infections remains an important way to prevent surgical site infections. **M. Honkanen, Clin Microbiol Infect 2019;25:1021**

Introduction

Periprosthetic joint infection (PJI) is a catastrophic complication of joint replacement surgery [1]. Therefore, it is essential that adequate preventive measures are taken before any elective joint replacement operation.

Active infections, including skin and urinary tract infections, at the time of operation are considered as potential risk factors for subsequent surgical site infection (SSI), and their treatment is therefore recommended [2]. Furthermore, active preoperative screening and treatment of dental infections is recommended [2–4].

Staphylococcal skin and nasal colonization is common among patients before elective joint replacement [5,6]. Thus, even without the presence of active infection, preoperative decolonization may reduce the incidence of SSIs caused by *Staphylococcus aureus* [6–9]. The use of oral antibiotics can reduce *S. aureus* carriage [10], but oral antibiotics may not reach sufficient nasal concentrations for effective decolonization. Therefore, they are recommended for decolonization of methicillin-resistant *S. aureus* (MRSA) only in conjunction with topical agents [11,12].

Although perioperative intravenous antibiotics have a well-established role in the prevention of SSIs [13,14], no studies have been conducted on the use of preoperative oral antibiotic before

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joint replacement surgery and its effect on the risk for subsequent SSI or PJI. The aim of this study was to investigate how patients' preoperative use of antibiotics affects the risk for PJI in a 1-year follow-up.

Patients and methods

This retrospective study was performed in the Coxa Hospital for Joint Replacement, Tampere, Finland. Patients, who had undergone an elective primary hip or knee replacement between September 2002 and December 2013 were identified from the local prospective joint replacement database. Patient consent is not required in retrospective studies like this, according to the Finnish national legislation. In patients with multiple joint replacements during the study period, each operation was considered separately. Until 2007, patients considered to have high risk for MRSA carriage were screened for MRSA. From 2008 onwards all patients were screened for MRSA on admission, but not for methicillin-sensitive *S. aureus* [15]. Routine preoperative skin and nasal decolonization was not used. All patients had preoperative clinical evaluation and laboratory tests at the operating hospital within 2 months before the surgery. Preoperative urine samples were taken routinely and 25% of the patients with bacteriuria received antibiotics [16]. A single dose of cefuroxime was used as perioperative antibiotic prophylaxis. If this was contraindicated, clindamycin or vancomycin was used. Known MRSA carriers received cefuroxime and vancomycin. Cemented prostheses were fixed with gentamicin-impregnated bone cement.

The courses of antibiotics (identified based on their ATC codes [17]; Table S1) purchased within 90 days before the joint replacement were identified from the prescription register of the Social Insurance Institution of Finland. The type of antibiotic and the date of purchase were recorded. Antibiotics are not available without a prescription in Finland and all purchases are recorded in this nationwide prescription register. Antibiotics given for inpatients could not be identified.

Patients with a valid entitlement to reimbursement for certain chronic diseases (diabetes, rheumatic diseases, hypertension, chronic heart failure, chronic coronary disease, arrhythmias, chronic lung disease, Parkinson's disease, epilepsy, Alzheimer's disease, psychotic disorders, haematological, and solid malignancies) at the time of the joint replacement were identified from the reimbursement register of the Social Insurance Institution of Finland (see a more detailed description in a previous study of the same study population [16]). For the analyses, chronic heart failure, chronic coronary disease, and arrhythmias were grouped together, as were Parkinson's disease, epilepsy, Alzheimer's disease, and psychotic disorders.

Patients' weight and height were retrieved from the joint replacement database to calculate body mass indexes (BMIs). The data on the types of prostheses, municipality of residence and indication of surgery was also gathered from the database. MRSA carriers were identified from the official database of carriers of multidrug resistant microbes in Pirkanmaa Hospital District.

The primary outcome was the occurrence of PJI. The occurrence of any surgical site infection (superficial or deep incisional infection or PJI) was considered as a secondary outcome. These infections were identified from prospective post-discharge surveillance data gathered by an infection control nurse according to the Centers for Disease Control and Prevention criteria [18] and National Nosocomial Infection Surveillance system methodology adapted for Finland [19]. The follow-up was 1 year for all operated joints. Microbiological data on the pathogens causing PJIs were collected from the electronic records of the microbiology laboratory.

Statistical analysis

All data analyses and management were performed using SPSS for Windows 23.0 statistical software package. Categorical variables were compared with chi-square test and continuous variables (age) with Student's independent-samples *t*-test. A value of $p < 0.05$ was considered statistically significant.

The association between preoperative antibiotic use and the outcome (PJIs and all infections separately) was first examined using univariate logistic regression analysis, and odds ratios and 95% confidence intervals (CI) were calculated. Then, a multivariable model was developed to account for possible confounding factors. Patients' gender, operated joint, age, BMI, use of cement in the operation, indication for surgery (osteoarthritis, rheumatic disease, previous trauma, and other reasons), and chronic diseases (chronic heart disease, chronic lung disease, diabetes, hypertension, malignancy, neurological or psychiatric disorder, and rheumatic disease) were all included in the model. Patients with the use of antibiotics with potential activity against staphylococcal species (i.e. amoxicillin–clavulanate, cephalosporins, clindamycin, flucloxacillin, fluoroquinolones, macrolides, tetracyclines, trimethoprim, and trimethoprim/sulfamethoxazole) [20] were examined separately.

Propensity scores were calculated using variables associated with preoperative antibiotic use ($p < 0.05$, Table 1). Patients were matched using nearest neighbour matching with calliper width 0.02 (0.2 of the standard deviation of the logit of the propensity score) resulting in 4106 matched pairs. A logistic regression analysis was performed also in the matched patient population.

Results

In total, there were 23 171 primary joint replacements performed for 17 562 patients. Table 1 shows the general characteristics of the study population. During the 1-year follow-up, 158 PJIs occurred in the study population (incidence 0.68%). Overall, 490 surgical site infections (2.11%) were identified.

Table 1
Characteristics of patients with and without preoperative oral antibiotic use

Patient characteristic	Patients with antibiotic use ($n = 4106$)		Patients without antibiotic use ($n = 19\,065$)		p
	n	%	*n*	%	
Male gender	1324	32	7486	39	<0.001
Age, years, mean (SD)	66	(11)	67	(11)	0.20
Knee location	2383	58	10 588	56	0.003
BMI, mean (SD)	29.7	(5.3)	29.2	(5.1)	0.001
Known MRSA-carrier	16	0.4	46	0.2	0.10
Rural living location	493	12	2649	14	0.001
Chronic diseases					
Chronic heart disease[a]	1577	38	6241	33	<0.001
Chronic lung disease	375	9	1140	6	<0.001
Diabetes	414	10	1463	8	<0.001
Hypertension	1285	31	5031	26	<0.001
Malignancy	182	4	625	3	<0.001
Neurological or psychiatric disorder[b]	180	4	687	4	0.02
Rheumatic disease	264	6	948	5	<0.001
Osteoarthritis as the indication for operation	3740	91	17 265	91	0.29
Use of cement in the operation	3123	76	14 287	75	0.17

[a] Includes chronic heart failure, chronic coronary disease and arrhythmias.
[b] Includes Parkinson's disease, epilepsy, Alzheimer's disease and psychotic disorders.

In total, 4106 (18%) of the joint replacements were preceded by one or more courses of oral antibiotics within 90 days before the operation. In 989 (4.3% of the study population) cases, there were two or more antibiotic courses. The median number of days between the joint replacement and the antibiotic course was 30 (Fig. 1). The most commonly used antibiotics were first-generation cephalosporins, penicillin, and pivmecillinam (Table 2). In total, there were 5741 packages of antibiotics purchased preoperatively, giving an antibiotic consumption of 2.75 packages per 1000 patients per day.

The incidence of PJI was 0.29% (12/4106) for patients with preoperative oral antibiotic use and 0.77% (146/19 065) for patients without antibiotics. A preoperative oral antibiotic course was associated with a decreased risk for subsequent PJI (Table 3). Also, in the propensity matched patient population, the risk for PJI was also lower for patients with antibiotic use (OR 0.34, 95% CI 0.18–0.65). The results were similar when antibiotic use within 30 days was considered: the incidence of PJI was 0.19% (4/2066) for patients with antibiotic use and 0.73% (154/21 105) for those without.

Of the twelve cases of PJI with preoperative oral antibiotic use, six were early infections, occurring within 30 days from the joint replacement. Overall, 34% (54/158) of the PJIs were early infections. The organism causing the PJI was identified in five cases with preoperative antibiotic use: in two cases it was *Staphylococcus aureus*, in two cases a coagulase-negative staphylococcus and one case was polymicrobial (a coagulase-negative staphylococcus and *Enterococcus faecalis*) (Table S2). The remaining cases (7/12, 58%) were culture-negative. On the other hand, 16% (23/146) of the PJIs in patients without antibiotic use were culture-negative.

When superficial infection cases were also included in the analysis, preoperative antibiotic use did not affect the overall risk for surgical site infection: the incidence was 1.90% (78/4106) for patients with antibiotic use and 2.16% (412/19 065) for patients without antibiotic use (OR 0.88, 95% CI 0.69–1.12).

No single antibiotic agent or antibiotic group reduced the risk for PJI statistically significantly (Table 2). However, when compared with patients without antibiotic prescriptions, the risk for PJI was lower for patients with anti-staphylococcal antibiotics (OR 0.34, 95% CI 0.16–0.72), but not for patients with the use of other antibiotics (OR 0.46, 95% CI 0.19–1.13).

A lower incidence of PJI for patients with antibiotic use was observed also when the analyses were repeated in the subgroups of hip and knee joint replacements, operations with and without the use of cement, patients with osteoarthritis as the indication for surgery, and the year of operation (Table S3). Statistically significant differences, however, were not always observed due to insufficient statistical power.

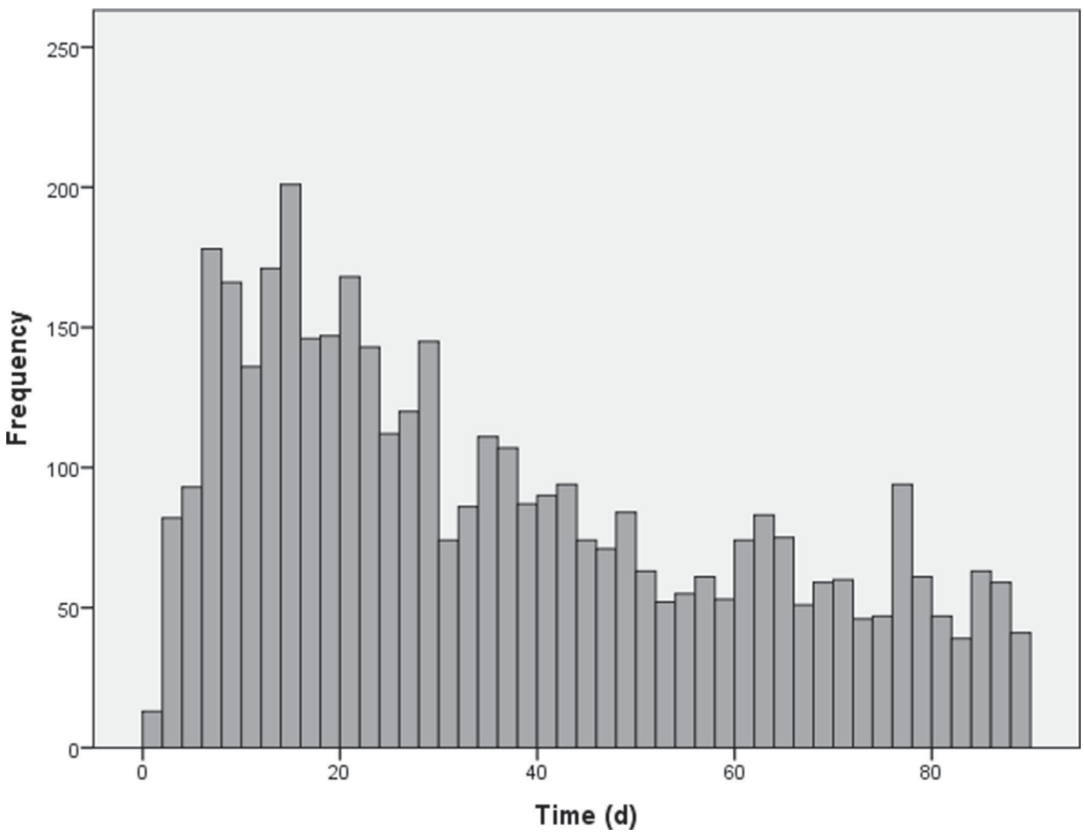

Fig. 1. The time difference (in days) between the joint replacement surgery and the date of purchase of the antibiotic course received closest to the surgery.

Table 2
The numbers of primary joint replacement operations preceded by different groups of antibiotics 90 days before surgery and their effect on the risk for periprosthetic joint infection (PJI)

Antibiotic group	Number of operations preceded by antibiotic use		Effect of antibiotic on the risk for PJI in the univariate analysis	
	N	% of all operations	OR	95% CI
First-generation cephalosporins	984	4.2	0.29	0.07–1.16
Penicillin	693	3.0	0.41	0.10–1.67
Pivmecillinam	571	2.5	0.51	0.13–2.05
Amoxicillin	544	2.3	0.53	0.13–2.15
Fluoroquinolones	500	2.2	0.58	0.14–2.35
Tetracyclines	424	1.8	NA[a]	NA
Macrolides	374	1.6	0.78	0.19–3.16
Trimethoprim	303	1.3	NA[a]	NA
Amoxicillin-clavulanate	182	0.8	NA[a]	NA
Clindamycin	146	0.6	1.01	0.14–7.23

[a] There were no PJIs in this group.

Table 3
The effect of preoperative oral antibiotic use on the risk for developing a PJI

	Univariate analysis		Multivariable analysis	
	OR	95% CI	OR	95% CI
Antibiotic use 30 days preoperatively	0.26	0.10–0.71	0.24	0.08–0.77
Antibiotic use 90 days preoperatively	0.38	0.21–0.69	0.40	0.22–0.73

Discussion

This large study shows that the use of oral antibiotics before elective joint replacement surgery is common. Also, the use of antibiotics preoperatively is associated with and may have an effect on the subsequent risk for periprosthetic joint infection.

In this study population, almost one fifth of the patients had received oral antibiotics within three months before surgery. The use of oral antibiotics prior to joint replacement surgery has hardly been studied. In a Swedish study [5], 25% of the patients coming for elective joint replacement had received antibiotics within 6 months before surgery, a number similar to the present study. This study indicates that patients having elective joint replacement seem to receive more antibiotics than the general population. According to European Centre for Disease Prevention and Control, the overall antibiotic consumption in Finland has been about two packages per 1000 inhabitants per day in the recent years [21], whereas in this study the number was 2.75 packages per 1000 patients per day.

The incidence of PJI was lower among patients with preoperative oral antibiotic use than among patients without antibiotic use. The effect of oral antibiotic use on the risk for PJI has not been studied before and thus this is a novel finding. Treatment of active infections before joint replacement surgery is recommended [2] to prevent haematogenous spread to the replaced joint postoperatively from non-treated infection sites. However, treatment of active infections should decrease the risk for PJI to the level of the general population, but not offer any additional prophylactic protection. Furthermore, active infections would probably lead to delaying the surgery.

Preoperative oral antibiotic use could possibly reduce the frequency of *Staphylococcus aureus* carriage. Supporting this view, the current study indicates that especially the use of staphylococcal antibiotics seemed to reduce the incidence for PJI. It has been estimated that 25% to 40% of the population are nasal carriers of *Staphylococcus aureus* [6,10], and similar numbers have been found among patients with joint replacement surgery [5,8]. In addition, nasal carriage of *S. aureus* is an independent risk factor for subsequent surgical site infection after joint replacement surgery [22] and different preoperative decolonization regimens have been proposed, including nasal mupirocin ointment with or without skin decolonization [6]. In a systematic review, Chen *et al.* [8] found that surgical site infection rates could be reduced by 13% to 200% with decolonization programmes [8]. However, most of the studies included in the review involved only patients, who screened positive for *S. aureus*. On the other hand, Sousa *et al.* found in a small randomized controlled trial that decolonization was not effective in reducing the rate of PJI [23], and the international consensus statement on PJIs does not recommend universal screening and decolonization of patients undergoing joint replacement surgery [2]. Unfortunately, there is no information on the rate of *S. aureus* carriage in the present study population and therefore the effect of the use of oral antibiotics on the risk of PJI in relation to the carriage rate could not be examined.

On the other hand, it has been proposed that oral antibiotics may not reach sufficient concentrations in the nares for adequate decolonization [12]. Nevertheless, studies on MRSA colonization have shown that carriage of *S. aureus* outside the nasopharynx is also common [24,25], even though the role of oral antibiotics in reducing carriage in non-nasal sites is unclear. Furthermore, it is unclear how long the potential effect of oral antibiotics in *S. aureus* decolonization could last. In a study conducted among children with skin infections and *S. aureus* colonization, oral antibiotics reduced the carriage rate by half for up to 50 days after the course of antibiotics [26].

Another possible mechanism for action for the antibiotics could be that the patients had 'hidden' infections that were treated, but this seems unlikely. For example, treating bacteriuria with antibiotics has been shown to be ineffective in the prevention of PJI in the same study population [16].

There are some limitations to this study. Firstly, the indications for the antibiotics were not known, nor who had prescribed the antibiotics. As the dosage of the antibiotics was not registered, antibiotic consumption rates based on defined daily doses could not be evaluated, but information on the number of pills purchased was available. Nevertheless, as all antibiotic purchases are recorded in the national register, patients' use of antibiotics could be evaluated comprehensively. Secondly, antibiotics given in hospitals could not be identified. However, it can be assumed that this number is fairly low, since the joint replacement surgery would have been most likely postponed if the patient had required treatment for an infection in a hospital setting. Thirdly, there could be a so-called 'healthy patient bias', where healthier patients are more prone to take care of themselves and perhaps seek medical attention more readily, thus potentially receiving antibiotics more easily than others. However, the characteristics and distribution of chronic diseases of patients with and without antibiotic use were similar, and the effect of chronic diseases could be considered extensively. Finally, it is possible that the association between oral antibiotic use and lower risk for PJI could be caused by some unknown confounding factors that could not be identified in the analysis. Nevertheless, the effect of many known risk factors for PJI could be taken into account and the results remained the same also in the propensity score-matched patient population.

While this study indicates that preoperative antibiotic use is associated with a lower rate of PJI, the use of oral antibiotics as prophylaxis cannot be recommended, unless there are active infections, due to potential harms, such as the increased risk for *Clostridioides difficile* infections and incidence of resistant bacterial strains. For example, Cheng *et al.* have shown that the use of non-

MRSA antibiotics increases the rate of nasal MRSA carriage [27]. In addition, even if used, the current study shows that the number needed to treat (NNT) with preoperative oral antibiotics to prevent one case of PJI would be high (NNT 211).

In conclusion, the use of oral antibiotics before elective joint replacement surgery is common and it may affect the subsequent risk for PJI, perhaps due to a reduced rate of *S. aureus* carriage. Further studies are needed in order to evaluate the significance of this novel result. Meanwhile, indiscriminate use of antibiotics before elective joint replacement surgery cannot be recommended, whereas treatment of active infections remains important in the prevention of surgical site infections.

Transparency declaration

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.cmi.2018.12.038.

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PUBLICATION IV

Periprosthetic joint infections as a consequence of bacteremia

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MAJOR ARTICLE

Periprosthetic Joint Infections as a Consequence of Bacteremia

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Background. The risk for developing a periprosthetic joint infection (PJI) during bacteremia is unclear, except for *Staphylococcus aureus* bacteremia. The aim of this study was to examine the risk for developing a PJI during bacteremia and to identify possible risk factors leading to it.

Methods. Patients with a primary knee or hip joint replacement performed in a tertiary care hospital between September 2002 and December 2013 were identified (n = 14 378) and followed up until December 2014. Positive blood culture results during the study period and PJIs were recorded. PJIs associated with an episode of bacteremia were identified and confirmed from patient records. Potential risk factors for PJI among those with bacteremia were examined using univariate logistic regression.

Results. A total of 542 (3.8%) patients had at least 1 episode of bacteremia. Seven percent (47/643) of the bacteremias resulted in a PJI. Development of a PJI was most common for *Staphylococcus aureus* (21% of bacteremias led to a PJI) and beta-hemolytic streptococci (21%), whereas it was rare for gram-negative bacteria (1.3%). Having ≥2 bacteremias during the study period increased the risk for developing a PJI (odds ratio, 2.29; 95% confidence interval, 1.17–4.50). The risk for developing a PJI was highest for bacteremias occurring within a year of previous surgery. Chronic comorbidities did not affect the risk for PJI during bacteremia.

Conclusions. The development of a PJI during bacteremia depends on the pathogen causing the bacteremia and the timing of bacteremia with respect to previous joint replacement surgery. However, significant patient-related risk factors for PJI during bacteremia could not be found.

Keywords. bacteremia; prosthetic joint infection; risk factors; *Staphylococcus aureus*; streptococci.

Hematogenous periprosthetic joint infections (PJIs) are due to hematogenous spread from another infection site and can occur at any time after joint replacement surgery [1, 2]. Late PJIs are usually hematogenous, but there is no consensus on the definition of late PJI. According to the traditional definition by Coventry et al., they occur 2 years after surgery or later [3]. However, other studies have used time limits from 3 [4] to 12 months [5]. Late acute PJIs are also characterized by an asymptomatic postoperative period before the onset of symptoms of infection. The proportion of late hematogenous PJIs has been estimated to be 13%–27% of all PJIs [6–10], whereas the overall incidence of late PJIs is around 0.25%–0.7% [5, 6, 8, 9, 11, 12] or 0.069% per prosthesis-year [10].

The origin of hematogenous PJIs can be from the skin and soft tissues, urinary tract, dental sources [4, 5], cardiovascular system [13], lungs [11], or the gastrointestinal tract [14]. Although most PJIs are caused by either coagulase-negative staphylococci or *Staphylococcus aureus*, hematogenous PJIs are mostly caused by *S. aureus*, followed by streptococci and gram-negative bacteria [1, 2, 15–17].

According to previous studies, 25%–40% of patients with *Staphylococcus aureus* bacteremia (SAB) and a joint replacement develop a hematogenous PJI [18–22]. The presence of 3 or more joint replacements increased the risk for PJI considerably during SAB in 1 study [21], but other studies have not been able to show patient-related risk factors for developing a PJI during SAB [20]. The risk for developing a PJI during bacteremia caused by other pathogens is unclear, as most reports on PJIs during bacteremia have been case studies [23–26]. Uçkay et al. reported a PJI rate of 6% in patients with any bacteremia [14]. Risk factors for developing a PJI during any bacteremia have not been studied.

The aim of this study was to examine the risk for developing a PJI during bacteremia caused by different pathogens and to identify possible risk factors leading to it.

METHODS

This is a retrospective study that was performed at the Coxa Hospital for Joint Replacement, Tampere, Finland. Patients from Pirkanmaa Hospital District (population ca. 500 000 inhabitants) who had a primary knee or hip replacement

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performed between September 2002 and December 2013 at the hospital were identified from the hospital database (see Figure 1 for a description of the study patients). Patients could have had additional primary hip and knee replacements (performed elsewhere or before the study period), but information on these was not available. The follow-up period for each patient was from the date of the first joint replacement surgery during the study period to the date of death or December 31, 2014, whichever occurred first. According to national legislation, patient informed consent was not required due to the retrospective design of the study. Institutional permission to conduct this study was granted by the authorities responsible for the patient records.

All positive blood culture results of the study patients occurring after the primary surgery until December 31, 2014, were obtained from the electronic records of the accredited microbiology laboratory of Tampere University Hospital. Positive blood cultures caused by coagulase-negative staphylococci, corynebacteria, micrococci, or *Cutibacterium* species were considered significant only if there was growth on 2 blood culture bottles (n = 28); otherwise, they were defined as contaminants (n = 89). Positive blood cultures by other pathogens were considered significant regardless of the number of positive culture bottles. All consecutive positive blood cultures with the same organism taken within 7 days of the first positive sample were considered part of the same episode of bacteremia.

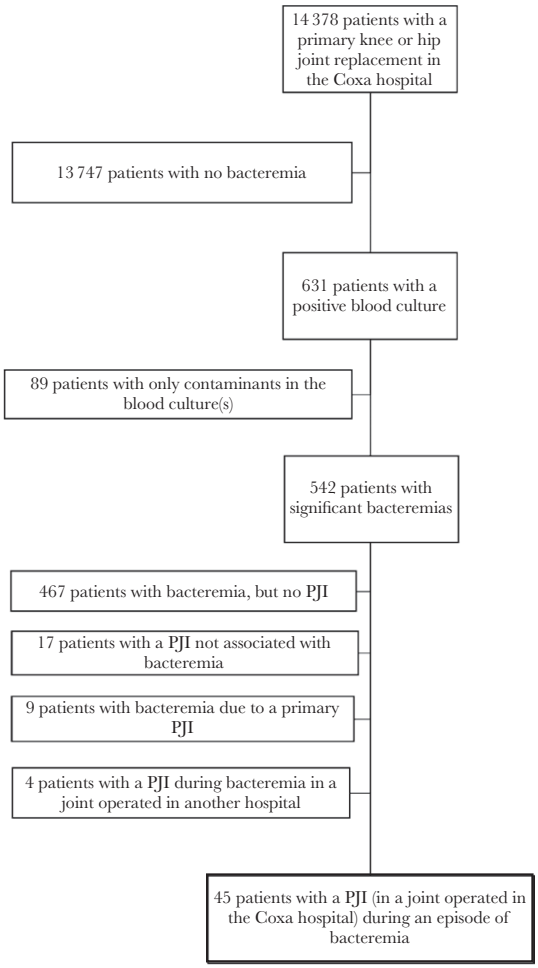

Figure 1. Description of the study patients. Abbreviation: PJI, periprosthetic joint infection.

PJI cases were identified from 6 different data sources: (1) prospective surveillance data from the national Finnish Hospital Infection Program of the National Institute of Health and Welfare, (2) postdischarge surveillance data gathered by an infection control nurse, (3) positive bacterial cultures of joint aspirates or tissue cultures from samples taken at the Coxa Hospital for Joint Replacement, (4) hospital discharge records with a diagnosis code of PJI (ICD-10 diagnosis code T84.5 or T81.4), (5) local joint replacement database records on revision arthroplasties performed due to PJI, and (6) Coxa's own infection register. A detailed description of these data sources can be found in a previous study of the patient population [27]. If the PJI occurred in a joint that was replaced outside of the study period (n = 4), it was not included in the analyses (but the patients remained in the study cohort, as they had other joints replaced at the Coxa hospital during the study period).

Patients with the same organism cultured from blood and from the affected joint were considered to have a PJI as a consequence of bacteremia. Cases where the PJI was determined to be the source of the bacteremia, based on the timing of symptom onset, were identified from the patient charts (n = 9) by 1 of the authors (M.H.) and were not included in the analyses. If the patient had a culture-negative PJI and bacteremia, patient charts were also reviewed. If the treating clinicians considered the PJI to be caused by the pathogen identified in the blood culture, it was recorded as such. Also, patient charts of patients who had a long duration (>7 days) between the positive blood culture and identification of the PJI were checked to verify the association.

Information on patients' chronic diseases (diabetes, rheumatic diseases, chronic heart failure, chronic coronary disease, arrhythmias, and chronic lung disease) was gathered from the drug reimbursement register of the Social Insurance Institution of Finland. For the statistical analyses, chronic heart failure, chronic coronary disease, and arrhythmias were grouped together (chronic heart disease). Information on body mass index (BMI), indication for joint replacement surgery, use of (antibiotic-impregnated) cement in the surgery, and date of death was gathered from Coxa's electronic database.

Statistical Analysis

All data analyses and management were performed using the SPSS for Windows 25.0 statistical software package.

The incidence of bacteremia and PJI was calculated as the incidence rate per 1000 person-years. Incidence of PJI as a consequence of bacteremias caused by different pathogens was calculated. Means or medians were calculated for continuous variables with a normal or skewed distribution, respectively.

The association between different potential risk factors (number of bacteremias, BMI, male gender, knee location, time since previous joint replacement surgery, age, indication for joint replacement surgery, use of cement in the operation, and chronic diseases) and the development of a PJI during bacteremia were examined for each joint separately. If the patient had multiple bacteremias during the study period, each was included in the analyses separately when analyzing the effect of age and time since previous joint replacement surgery on the risk for PJI. Potential risk factors were analyzed using binary logistic regression with univariate analysis, and odds ratios and 95% confidence intervals were calculated.

RESULTS

There were 14 378 patients with a primary knee or hip joint replacement performed during the study period. Of these, 4475 patients had more than 1 primary joint replacement. A total of 1346 patients had a revision arthroplasty performed during the study period. The mean follow-up time (range) was 6.0 (0–12) years.

During the study period, 542 (3.8%) patients had at least 1 episode of bacteremia after the primary joint replacement surgery, and 85 (0.6%) patients had more than 1 bacteremia. The maximum number of separate episodes of bacteremia per patient was 8 (1 patient). In total, there were 643 episodes of bacteremia. The incidence rate of bacteremia was 7.4 per 1000 person-years. The bacteremias occurred 3–4285 days after the first joint replacement operation (median, 1460 days); 13% occurred within 1 year (85/643) and 4% within 3 months (27/643). *Escherichia coli* was the most common causative pathogen (241/643, 37% of bacteremias). The distribution of pathogens causing the bacteremias is shown in Table 1.

There were in total 288 PJIs, and the incidence rate was 3.3 per 1000 person-years. Of the infections, 131 (45%) were early infections occurring within 90 days of the previous surgery, 53 (18%) occurred within 3–12 months, and 104 (36%) occurred after 1 year. The distributions of the PJIs over time for patients with and without bacteremia are shown in Figure 2A and B.

Of the episodes of bacteremia, 7% (46/643) resulted in a PJI (Table 1). One of these was a bilateral knee infection. Of the PJIs during bacteremia, 29 (62%) were in the knees and 18 (38%) in the hips. Seven PJIs occurred after revision joint replacement. One patient had 2 separate PJIs associated with different episodes of bacteremia. Thus, 45/542 (8%) patients with 1 or more episodes of bacteremia developed a PJI. The duration between the first positive blood culture and identification of the PJI ranged from 0 to 512 days (median, 2 days). There were 10 (21%) PJIs where the pathogen could not be identified from the affected joint, but these were considered to be caused by the pathogen identified in the blood culture. In most cases, these patients had received antibiotics before taking the samples for bacterial culture from the joint.

Table 1. Distribution of Pathogens Causing Bacteremia and PJIs Developed During Bacteremias

	Total No. of Bacteremias (n = 643)		No. of Bacteremias With a PJI (n = 46)	
Pathogen	No.	%	No.	%
Escherichia coli	241	37	3	1
Staphylococcus aureus	105	16	21[a]	20
Beta-hemolytic streptococci	58	9	12	21
Streptococcus pneumoniae	43	7	2	5
Coagulase-negative staphylococci	28	4	0	0
Enterococci	28	4	1	4
Klebsiella species	27	4	1	4
Viridans group streptococci	25	4	4	16
Other gram-negative bacteria[b]	46	7	0	0
Anaerobes	20	3	2	10
Yeasts	3	0.5	0	0
Other[c]	12	2	0	0
Polymicrobial	7	1	0	0

Abbreviation: PJI, periprosthetic joint infection.

[a]Includes 1 bilateral infection, which is counted as 1.

[b]Includes enterobacteriae, *Pseudomonas* species, *Proteus* species, *Morganella morganii*, *Citrobacter* species, *Haemophilus influenzae*, *Serratia marcescens*.

[c]Includes lactobacilli, *Listeria monocytogenes, Actinobaculum schaalii, Aerococcus urinae, Arcanobacterium pyogenes, Granulicatella adiacens*.

The development of a PJI during bacteremia varied between different pathogens (Table 1). It was most common for *Staphylococcus aureus*, beta-hemolytic streptococci, and viridans group streptococci, but rare for gram-negative bacteria and coagulase-negative staphylococci; 1.3% of bacteremias caused by gram-negative bacteria resulted in a PJI. There were 11 PJIs as a consequence of bacteremia that occurred within 3 months of the previous surgery. These infections were caused by *Staphylococcus aureus* (n = 3), viridans group streptococci (n = 2), *Streptococcus agalactiae* (n = 2), *Clostridium perfringens* (n = 2), *Klebsiella terrigena* (n = 1), and group G streptococcus (n = 1).

Having more than 1 bacteremia during the study period increased the risk for developing a PJI (Table 2). Also, the risk for developing a PJI was higher for bacteremias occurring less than a year after the previous surgery than for bacteremias occurring later. Gender, obesity (BMI ≥ 25), operated joint (hip, knee), indication for primary surgery, use of antibiotic-impregnated cement for prosthesis fixation, and chronic diseases did not

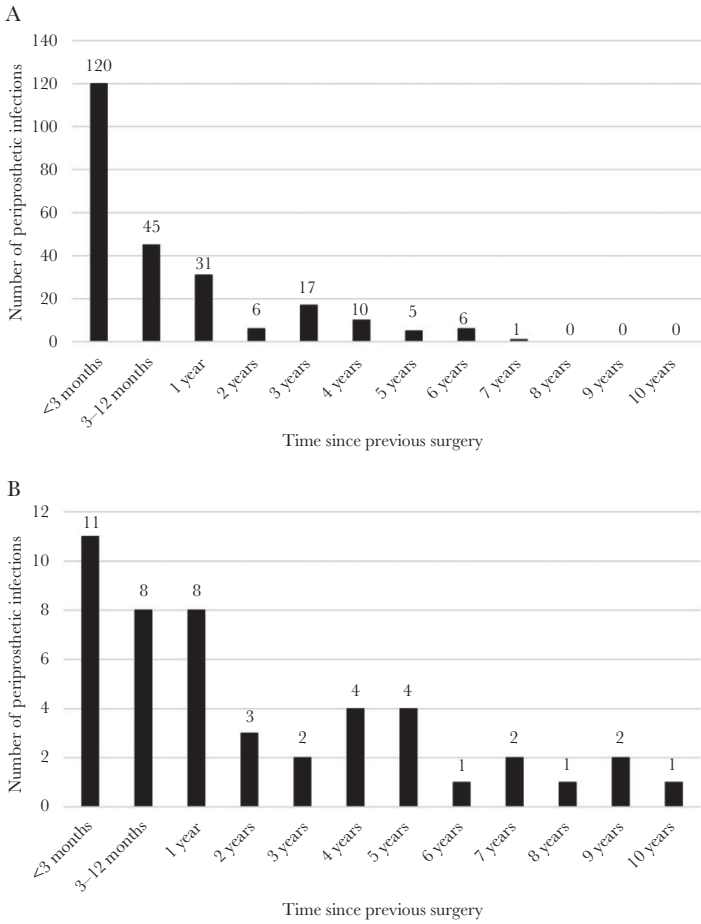

Figure 2. A, The distribution of periprosthetic infections over time in patients without bacteremia. B, The distribution over time of periprosthetic joint infections as a consequence of bacteremia.

affect the risk of developing a PJI as a consequence of bacteremia (Table 2). Older age was associated with a lower risk of developing a PJI, but when the effect of bacteremias caused by *E. coli* was taken into account in a multivariable analysis, the effect of patients' age was no longer statistically significant (odds ratio, 0.97; 95% confidence interval, 0.95–1.00).

DISCUSSION

This study shows that development of a PJI as a consequence of bacteremia is highly dependent on the type of pathogen causing the bacteremia. The risk was the highest in bacteremias caused by *Staphylococcus aureus*, beta-hemolytic streptococci, and viridans group streptococci and was associated with repeated episodes of bacteremia. On the other hand, the development of a PJI during bacteremia caused by gram-negative bacteria, especially *E. coli*, and coagulase-negative staphylococci, was rare. Patients with a bacteremia occurring within 1 year of previous surgery had a higher risk of developing a PJI than those with bacteremias occurring later.

In the current study, 7% of the episodes of bacteremia resulted in the development of a PJI, corresponding to the rate described by Uçkay et al. [14]. In their study, 6% (5/81) of bacteremias resulted in a PJI. Other studies examining the risk of developing a PJI during SAB [18–22] have reported slightly higher rates than in the current study. Uçkay et al. reported a rate of 2.9% for PJI during bacteremia caused by *E. coli*, 14% for SAB, and 40% for anaerobic bacteremia, but the number of PJIs as a consequence of bacteremia was so small (n = 5) that it is difficult to make meaningful conclusions from the results. No other studies have examined the risk of developing a PJI during bacteremia caused by pathogens other than *S. aureus*.

Table 2. Potential Risk Factors for Developing a Periprosthetic Joint Infection During Bacteremia

Risk Factor	Joints With PJI (n = 47)		Joints Without PJI (n = 672)		Odds Ratio	95% Confidence Interval
	No.	%	No.	%		
No. of bacteremias ≥2	13	28	96	14	2.29	1.17–4.50
BMI ≥25 kg/m^2	38	81	473	70	1.82	0.70–4.72
Chronic lung disease	3	6	33	5	1.32	0.39–4.48
Chronic heart disease	6	13	72	11	1.22	0.50–2.97
Male gender	21	45	276	41	1.16	0.64–2.10
Knee joint	29	62	398	59	1.11	0.60–2.04
Time since previous joint replacement, y[a]						
<1	17	36	94	12	1.00	
1–10	28	60	672	85	0.23	0.12–0.44
>10	2	4	24	3	0.46	0.10–2.13
Age at the time of bacteremia, mean (SD),[a] y	71	(11)	76	(10)	0.97	0.94–0.99
Rheumatic disease	3	6	59	9	0.71	0.21–2.35
Diabetes	5	11	103	15	0.66	0.25–1.70
Primary osteoarthritis as indication for primary joint replacement	43	92	588	88	0.65	0.23–1.86
Use of antibiotic-loaded cement in the primary operation	35	74	555	83	0.59	0.30–1.17

Abbreviations: BMI, body mass index; PJI, periprosthetic joint infection.

[a]Calculated for each bacteremia and joint (n = 837) separately.

Interestingly, the risk of PJI was similar for bacteremias caused by *Staphylococcus aureus* and beta-hemolytic streptococci. However, it is not surprising, as streptococci have been reported to cause a considerable proportion of late hematogenous PJIs [1, 2, 16]. On the other hand, there were no PJIs during bacteremia caused by coagulase-negative staphylococci, even though they are significant pathogens that cause PJIs [1]. Coagulase-negative staphylococcal bacteremias are mostly nosocomial [28], and it has been shown that nosocomial SABs are not associated with PJIs [20, 21], making it likely that this is the case for coagulase-negative staphylococci as well. Unfortunately, the differentiation between community-acquired and nosocomial bacteremias was not possible in this study. Despite the commonness of urosepsis caused by *E. coli*, especially in the oldest age groups, it rarely leads to the development of a PJI. Thus, patients with bacteremia caused by gram-negative bacteria do not warrant the special attention with respect to the development of a PJI paid to those with bacteremias caused by *S. aureus* or beta-hemolytic streptococci.

This study demonstrates that viridans group streptococci can lead to the development of a hematogenous PJI, even though the absolute number was low. These bacteria are associated with dental or gastrointestinal sources [29, 30]. Unfortunately, due to the retrospective nature of the current study, patients' dental status or previous dental procedures with or without antibiotic prophylaxis could not be evaluated, and thus conclusions on the risk for PJI after dental procedures could not be made.

No patient-related risk factors for the development of a PJI during bacteremia, such as chronic diseases, could be identified, and this has been the case in previous studies as well [14, 20]. However, having more than 2 bacteremias during the study period increased the risk of developing a PJI during bacteremia. This possibly reflects some unidentifiable factor that increased patients' susceptibility to infection in general. Patients' use of immunosuppressive medication was not evaluated, but rheumatic diseases did not increase the risk for developing a PJI during bacteremia, nor did diabetes. An important observation, instead, is that the risk for developing a PJI as a consequence of bacteremia was highest for bacteremias occurring within 1 year of previous surgery. Large studies have shown that the overall risk of developing a PJI is highest for the first 2 years after surgery [7–9], and this is probably partly due to the increased risk for hematogenous PJIs. On the other hand, in a study by Rakow et al., most of the hematogenous PJIs occurred after 2 years from primary surgery [13].

There are some limitations to this study. First, some of the patients could have had joint replacement surgery performed elsewhere, before the study period began, and thus all prosthetic joints at risk for infection could not be identified. In addition, there might have been other patients in the Pirkanmaa hospital district with joint replacements inserted at other hospitals who developed PJIs during bacteremia, but they could not be identified, and this might have resulted in lower incidence numbers. However, as the number of patients with surgery performed elsewhere was probably not very high, its effect can be assumed to be insignificant. Second, due to the retrospective nature of this study, some of the data, such as dental procedures, were not available. To avoid other limitations related to retrospective data collection, such as missing PJI cases, multiple data sources were used. In addition, the source of bacteremia could not be investigated, and differentiation between recurrent and relapsing bacteremia was not possible in cases with multiple

episodes of bacteremia. Third, it is impossible to say with absolute certainty whether all PJIs attributed to bacteremia were truly so, but patient charts were reviewed carefully to minimize this error. The pathogens causing the early PJIs during bacteremia were not typical pathogens causing primary PJIs, thus supporting the fact that these PJIs were truly consequent to the bacteremia. Finally, as there was a limited follow-up period for each joint (maximum 12 years), PJIs as a consequence of bacteremia occurring after the study period were missed, thus potentially affecting the incidence numbers.

In conclusion, this large study shows that the type of pathogen, history of infections, and timing of bacteremia should be taken into account when evaluating the risk of PJI in a patient with bacteremia. Developing a PJI during an episode of bacteremia caused by *Stapylococcus aureus* or beta-hemolytic streptococci is fairly common, and viridans group streptococci can lead to PJIs during bacteremia. This should be taken into account when a patient with a joint replacement presents with bacteremia caused by these agents, especially during the first postoperative year. Although diabetes, rheumatoid arthritis, and chronic heart and lung diseases did not affect the risk of PJI, there is possibly some unknown factor that increases patients' susceptibility to infection in general and thus also to developing a PJI during bacteremia.

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