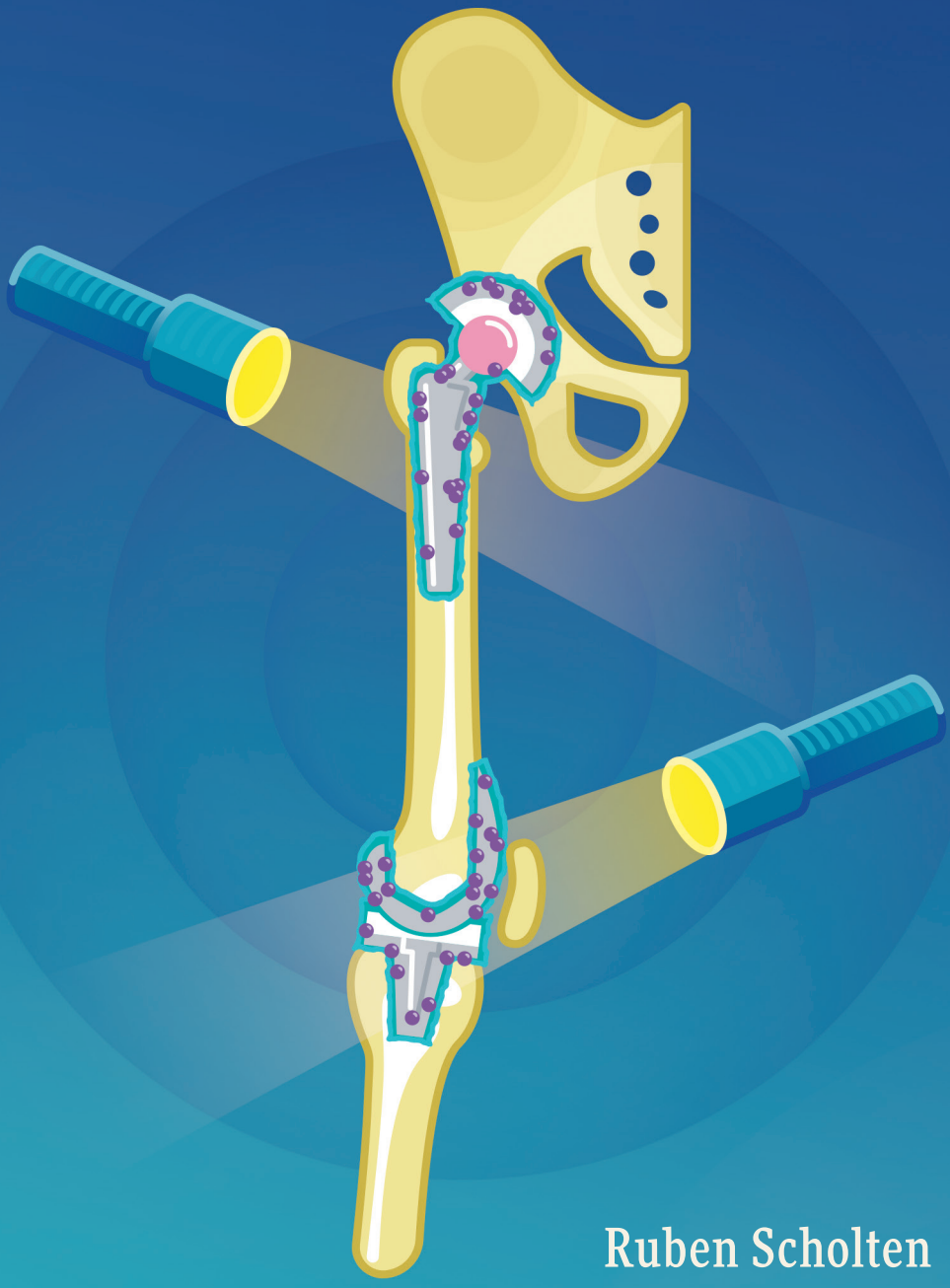
Elucidating Periprosthetic Joint Infections



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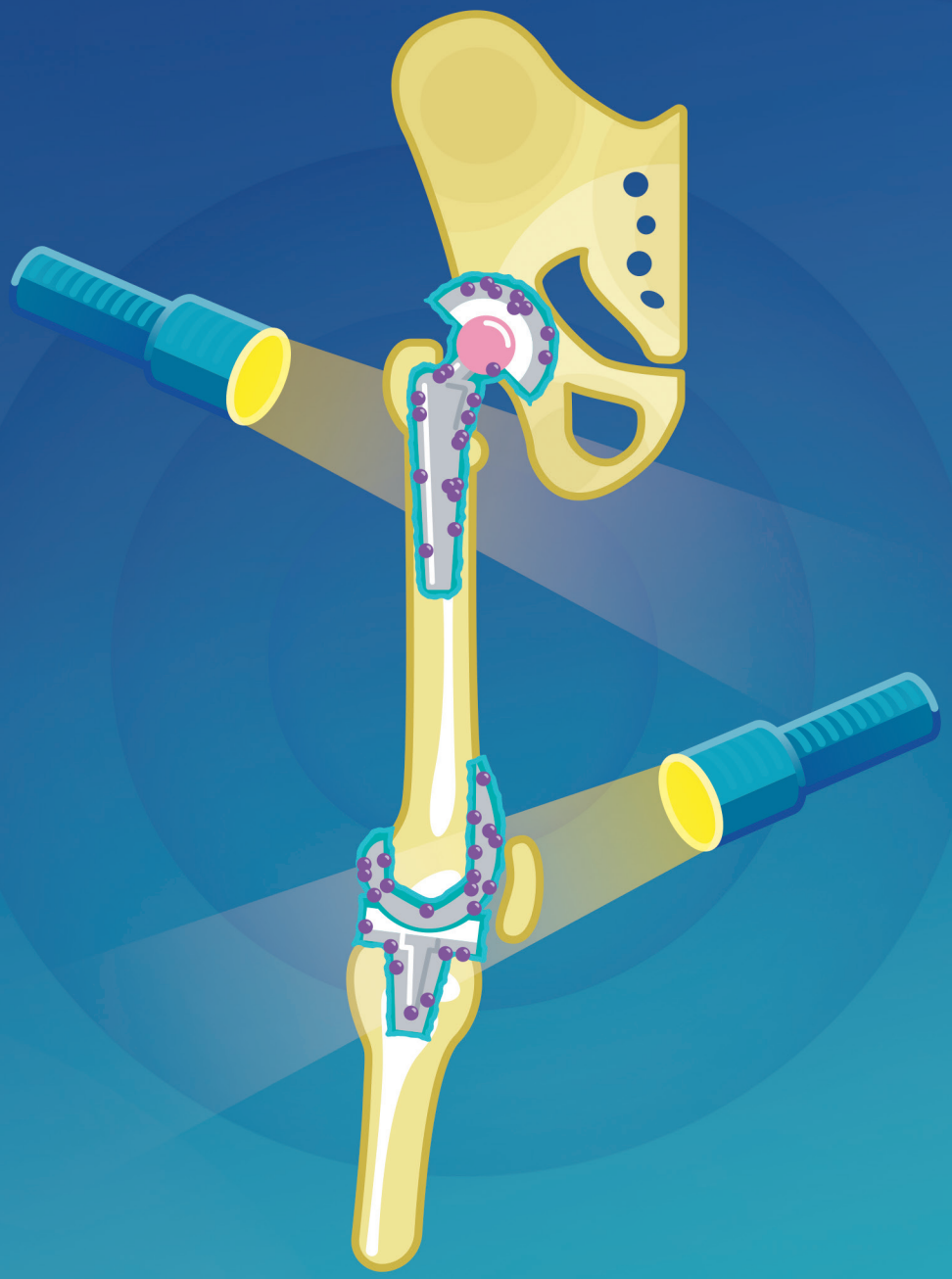

1

General introduction

ARTHROPLASTY

Total hip and total knee arthroplasty are performed worldwide in large numbers to treat degenerative joint disease. In the United States alone, more than 450.000 total hip and 800.000 total knees are performed annually. The goal of an arthroplasty procedure is to keep patients (usually suffering from degenerative joint disease) mobile without pain, thereby greatly improving quality of life.

Degenerative joint disease is a collective term for a variety of disorders that cause the destruction of joint cartilage, ultimately resulting in a painful and stiff joint. Conditions such as primary osteoarthritis, inflammatory arthritis including rheumatoid arthritis, posttraumatic degenerative joint disease, or osteonecrosis/joint collapse with cartilage destruction are included within degenerative joint disease, with primary osteoarthritis being the most prevalent.

OSTEOARTHRITIS

Osteoarthritis (OA) is a type of degenerative joint disease caused by the breakdown of joint cartilage. The disease affects about 1 in 7 adults in the United States and is believed to be the fourth leading cause of disability in the world (1). The disease results in pain and stiffness of the affected joint(s) usually progressing slowly over the course of several years. The knee is affected the most, followed by the hip joint and the joints in the hand (1).

Treatment initially consists of conservative measures, including exercise aided by a physical therapist, pain medications and/or adjustments to physical activities. Weight loss may help in those who are overweight. If conservative treatment fails to provide adequate pain relief, surgery is the next option. In young patients, an osteotomy around the hip or knee can be considered to reduce the complaints. However, joint replacement surgery usually is the preferred option regarding the treatment of osteoarthritic knee and hip joints. Joint replacement surgery techniques are now available for more than 50 years.

TOTAL JOINT ARTHROPLASTY

In the mid-nineteenth century, the first attempts to perform a joint arthroplasty were undertaken. The goal of the arthroplasty was to restore the (painfree) function and motion of a joint. These first attempts consisted of the resection of an ankylosed

arthritic joint which did not yield satisfactory results leading surgeons to try different approaches to solve the problem (2). These straightforward resection arthroplasties turned into interpositional arthroplasties in which other tissues (joint capsule, fat, skin, fascia) were placed between the resected joint surfaces (2). Results improved only marginally, so the quest for superior methods continued. Experimentation continued using several man-made substances instead of patient tissue ensued, including glass and celluloid, but none produced long-lasting good results (2). A major advancement in hip arthroplasty was achieved when Smith-Petersen developed the Vitallium (a cobalt-chrome-molybdenum alloy) mold interpositional arthroplasty of the hip in 1940 (figure 1) (3). Still, this technique was deemed to only provide satisfactory results in congenital hip dislocations (3).

Following the success of Smith-Peterson in hip dislocations, several surgeons developed implants to replace one side of the affected joint, usually the head of the femur (hemiarthroplasty) (2). Several materials were used, but metal soon became the material of choice for the femoral stem and head (2).

The next major breakthrough in hip arthroplasty was achieved in the 1960s by Sir John Charnley. Charnley performed an arthroplasty of the hip using the principle of total joint replacement (in which both resected sides of the joint are replaced) using a stemmed stainless-steel replacement of the femoral head and a high-density polyethylene (PE) implant on the acetabular side. He fixed these components to the bone using polymethylacrylate cement (4). A small 22 mm metal head was used in combination with the PE cup, thus a low friction arthroplasty was created.

Using this technique, for the first time Charnley achieved satisfactory results and his success did not go unnoticed. Charnley's concept was also applied by Gunston to perform total knee arthroplasty. Gunston was the first to recognize that the knee does not rotate on a single axis (like a hinge), but in fact rolls and glides which he tried to implement in his arthroplasty design (figure 2) (5). His results were superior to the hinged knee implants being used prior to this design but several limitations remained (6).

Charnley's (and Gunston's) basic concepts of total joint arthroplasty are still used in nearly all arthroplasty procedures up to now. (2). However, many improvements to the implant design of both TKA and THA have been implemented to further improve the outcome of both procedures (figures 3 and 4) (2). Currently, if properly implanted, total hip and knee arthroplasties achieve exceedingly high success rates with regard to the aforementioned goals of total joint arthroplasty (relieve pain, restore motion, provide stability and correct deformity) both in the short- and long term (2).

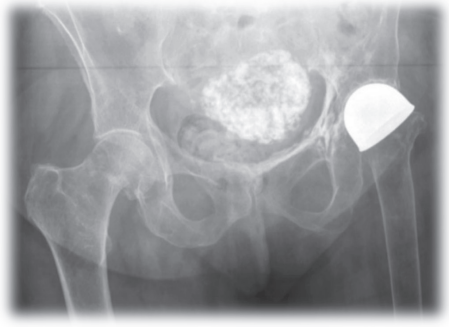

Figure 1: Smith-Petersons' hip arthroplasty. (7)

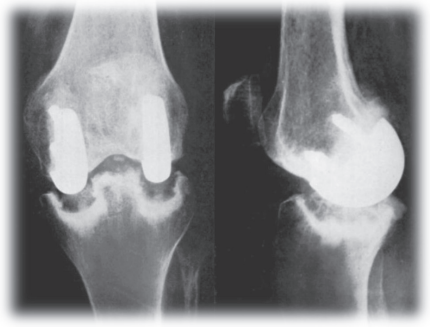

Figure 2: Front and side view of Gunston's total knee arthroplasty.

In fact, at the beginning of the 21st century, the results of hip arthroplasty surgery were deemed so good that the Lancet labeled the THA as the "operation of the century" (8). Nowadays, both primary total hip and knee implants have survival rates of more than 95 % at 10 years after the implantation.

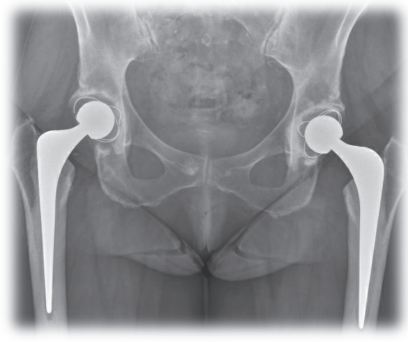

Figure 3: Modern bilateral THA.

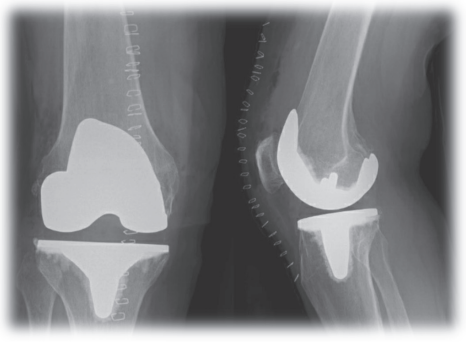

Figure 4: Front and side view of modern TKA.

Thanks to these great results, total hip arthroplasty (THA) and total knee arthroplasty (TKA) are regularly performed procedures for patients suffering from a range of degenerative joint conditions. In 2022, 36,707 primary THAs were performed in the Netherlands alone, along with 26,708 primary TKAs (9). With an ageing population, these numbers are expected to increase in the future.

PERIPROSTHETIC JOINT INFECTION

Unfortunately, despite the great functional results as well as impressive long time survival data, complications still occur in THA and TKA. One of the most devastating complications is a periprosthetic joint infection (PJI), which is an infection of the implanted material and the surrounding tissues. PJIs accounts for up to 25% of failed TKA and 15% of failed THA (10, 11).

The consequences of a PJI for the individual patient can be disastrous and its treatment remains a serious challenge to clinicians. Treatment of a PJI usually requires additional surgical procedures. The first option is most cases is a debridement, administration of antibiotics and implant retention (DAIR). During the surgical debridement procedure the modular components (in THA the head and insert and in TKA only the insert) are often exchanged. An alternative treatment, usually in case of failure of DAIR, is an exchange of the whole arthroplasty either as a one- or two-stage procedure.

All of these aforementioned surgical procedures need to be combined with a prolonged aggressive antibiotic treatment. Unfortunately, this is almost always accompanied by prolonged hospitalization and the serious side effects of chronic antibiotics usage. In case of treatment failure and an impossibility for reconstructive surgery, salvage operations can be performed. These include resection arthroplasty of the hip (a Girdlestone procedure, which is in fact the same as the resection arthroplasties performed in the mid-nineteenth century) or, in case of a failed TKA joint, knee fusion or even transfemoral amputation.

Apart from the disastrous consequences for the individual patient with PJI, there is also a huge economic burden associated with PJIs. Recently, a study predicted that the combined annual hospital costs related to PJI of the hip and knee in the United States will be about $1.85 billion ($753.4 million for THA PJI and $1.1 billion for TKA PJI) annually by 2030 (12).

Subtypes of PJI

Several different subtypes of PJI can be distinguished. PJI can be subdivided into early (<3 months after surgery), delayed (3-12 months after surgery) and late (>1 year after surgery) infections (table 1) (13). A separate type are the hematogenous infections.

Currently, it is believed that two thirds of all cases of PJI are caused due through the intraoperative inoculation of micro-organisms during the primary surgery when the implants are inserted (13). However, the subtype of PJI that ensues is dependent

Table 1: Overview of the PJI subtypes, their timing, expected pathophysiology and virulence.

PJI type	Probable pathophysiology	Virulence	Timing
Early	Intraoperative inoculation	High	< 3 months
Delayed	Intraoperative inoculation	Low	3 – 12 months
Late	Intraoperative inoculation	Low	> 12 months
Hematogenous	Hematogenous seeding	High	Any moment

on the virulence of the inoculated microbe. Highly virulent micro-organisms (e.g. Staphylococcus aureus, streptococci, enterococci) tend to cause early infections with obvious local and systemic signs of inflammation (14). Delayed infections usually present with more subtle signs including joint pain and in the longer term even implant loosening. These infections are usually caused by low-virulent organisms (e.g. coagulase-negative staphylococci or Cutibacterium species) (14). Often, these delayed PJIs do not present with the traditional signs of sepsis (e.g. fever, or elevated serum inflammatory markers), making the diagnosis more challenging.

PJI can also develop through hematogenous seeding of micro-organisms to the implant from a distant primary focus located elsewhere in the body. This subtype is generally referred as a hematogenous PJI. This can occur during the entire indwelling time of the implant, but the risk is higher in the first years after implantation. The latter is due to the high vascularity of the periprosthetic tissues during this initial period. Notably, the risk of developing an PJI following S. aureus bacteremia is reported to be as high as 34%. Patients with a hematogenous PJI typically present with acute onset of clinical symptoms after a pain-free post-operative period of the implanted prosthesis. Identifying the primary focus of infection in these cases is warranted to prevent infection relapse.

Treatment strategies of PJI

The treatment of a PJI is a serious clinical challenge and far more complex than the treatment of most soft tissue infections. The difficulty lies in the properties of (infected) bone which is even further deteriorated by the behavior of bacteria in the presence of a foreign body (the implanted prosthesis in case of THA or TKA). In fact, this foreign body allows the bacteria to better evade the immune system and antibiotics, often by producing a biofilm.

Infections of bones (septic osteomyelitis) and/or joints (septic arthritis) have always been a serious challenge to both orthopedic surgeons and infectiologists (2). The first

records on bone infections, now called osteomyelitis, date back to the time of Hippocrates (460-370 BC). In 1773, Broomfield called the disease "abscessus in medulla". The name osteomyelitis was proposed in 1844 by Nelaton (15).

In many bacterial diseases in soft tissues, a high treatment success rate has been established utilizing antibiotic therapy. However, this has never been achieved in bacterial infections of bones and joints. The latter is caused by the physiological and anatomical characteristics of bone (2). It is believed that other factors than the mere presence of bacteria in the bone need to be present in order to develop osteomyelitis. Osteomyelitis only seems to occur when an adequate number of virulent organisms overcome the hosts' defense (2). Local skeletal factors play a role in this process, as well as patient factors like concomitant diseases, a malnutrition status and inadequacies of the immune system (2).

Acute osteomyelitis generally includes a suppurative inflammation caused by bacteria (16). This inflammatory process results in tissue necrosis which in turn causes the destruction of bone. Subsequent compression and obliteration of vascular channels in the bone due to the infection process results in ischemia which can yield segments of bone devoid of a blood supply (16). These pieces of bone can form sequestra, in fact dead bone remnants, that continue to harbor bacteria since both antibiotics and inflammatory cells are unable to reach these avascular sequestra (16).

Before the discovery of antibiotics, osteomyelitis was treated only surgically (15). Surgery for osteomyelitis usually consisted of debridement, saucerization and wound packing allowing for secondary wound healing (15). Historically, the mortality of osteomyelitis in that era was around 30% (15). When penicillin was discovered in the 1940s, the mortality was reduced to about 10% (15).

Local skeletal (and surrounding soft tissue) factors are obviously altered by the invasive arthroplasty procedures, as well as through the implantation of a foreign body. On top of the latter, micro-organisms possess the ability to grow and adhere to artificial objects (or necrotic tissue) through the formation of a biofilm. Micro-organisms immediately adhere to the implants' surface on first contact. Initial growth of biofilm occurs through multilayer cellular proliferation, as well as cell-to-cell adhesion and starts in the first hours after infection. Mature biofilms take several weeks to develop and consist of complex 3D-communities where micro-organisms live clustered together in a highly hydrated, self-produced extracellular matrix. This biofilm protects the micro-organisms from environmental factors (e.g. antibiotics and the immune system cells) (14). In fact, micro-organisms protected by their biofilm are up to 1,000 times more resistant to growth-dependent antimicrobial agents than

their planktonic counterparts (14). To make things worse, clinical experience and several experimental studies demonstrate a high susceptibility to infection following arthroplasty procedures using artificial implant devices (16). This is underlined by the fact that even pathogens with low virulence can cause symptomatic infection in the presence of a foreign body (16). For example, the presence of a foreign body reduces the minimal infecting dose of *S. aureus* more than a 100,000-fold (17).

All in all, periprosthetic joint infection (PJI) remains a devastating complication after total joint arthroplasty (TJA). It is the most common indication for revision total knee arthroplasty (TKA), and the third most common reason for revision total hip arthroplasty (THA) despite the relatively low reported incidence of early PJI (ranging between 0.2% to 2.2%) for both THA and TKA (18-20).

Considering the expected increasing numbers of THAs and TKAs being performed annually due to an ageing population and an increasing prevalence of osteoarthritis due to co-morbidities like obesity, diabetes and an aging population (21) the incidence of PJI may very well increase in the future. Therefore, optimizing primary THA and TKA procedures with regard to the prevention of PJI should be imperative.

OUTLINE OF THIS THESIS

This thesis aims to enhance the further understanding of PJI after total joint arthroplasty, offering insights and recommendations on prevention, diagnosis, and treatment. The work presented in this thesis is subdivided into three parts:

I. Prevention
II. Diagnosis
III. Treatment

Part I - Prevention

Several modifiable risk factors are known that predispose to the development of PJI. These factors include e.g. poor glycaemic control, aneamia, obesity, malnutrition, carriership of certain micro-organisms and smoking. The risk of PJI may be reduced by perioperative strategies such as timely and appropriate dosage of prophylactic antibiotics, adequate skin preparation with chlorohexidine-based solution, the type of anesthesia, the prevention of intra-operative hypothermia, the presence of previous implanted devices (e.g. following previous surgery for a fracture) and irrigation of the wound with diluted betadine at the end of surgery (22). In this part of the thesis we assess the effects of hypothermia, carriership of certain micro-organism, previous implanted devices and the chosen type of anesthesia.

Hypothermia

Negative effects of perioperative hypothermia on the treatment outcome and the occurrence of complications have been described in various studies. Even mild perioperative hypothermia can increase the incidence of post-operative complications (increased mortality, sepsis, stroke, surgical site infection) (23). These effects can be considerable, a decrease of 1.9 ℃ in core temperature triples the relative risk of surgical site infection (SSI) and increases the duration of hospitalization by 20% (24). However, to date no association between hypothermia and PJI has been established. In **Chapter 2** we explored the potential association between peri-operative hypothermia and the incidence of PJI.

Nasal colonization of Staphylococcus aureus

Staphylococcus aureus has previously been identified as the most common micro-organism causing SSI and nasal carriage of *Staphylococcus aureus* appears to be a major risk factor for the development of SSI (25). Furthermore, eradication of nasal *Staphylococcus aureus* is demonstrated to be effective in reducing the incidence of SSI following a variety of surgical procedures (26). However, no consensus is established on whether this strategy is effective in reducing the actual number of true PJIs after hip or knee arthroplasty. As such, the available evidence regarding the effectiveness of these widely introduced and costly screening and eradication protocols in the context of TKA and THA remains controversial. In **Chapter 3** the (cost) effectiveness of a preoperative *Staphylococcus aureus* screening and eradication protocol in reducing the incidence of early PJI is assessed.

Hardware removal & THA

A systematic review reported on an increased risk for PJI following THA after a previously internal fixation of a proximal femoral fracture (27). However, more recent studies reported no increased risk for early PJI following salvage THA (28-30). Thus, there still appears to be a lack of consensus in the literature on a potential increased risk of PJI in case of concomitant hardware removal at time of THA. In addition, there is no consensus whether a one-stage procedure, combining implant removal and consecutive hip arthroplasty, or a two-stage procedure (with a certain time interval) should be advocated. **Chapter 4** will address the incidence of early PJI in THA following hardware removal, and to provide a comparative framework regarding the incidences of early PJI following either single-stage or two-stage THA combined with hardware removal.

Type of anesthesia

Despite the increasing awareness of the importance of PJI prevention, the role of procedure related factors such as the type of anesthesia, remains to be elucidated (31).

Remarkably, the notion that anesthesia may influence the immune response has been suggested as early as 1903 (32). Several recent studies suggested spinal anesthesia reduces the risk for SSI when compared to general anesthesia in THA and TKA (33, 34). However, others identified no associations between the type of anesthesia and surgical site infection (SSI) (35-37). Importantly, no studies assessing the role of anesthesia during THA and TKA with well-defined definitions of PJI have been performed. **Chapter 5** explores the relationship between the type of anesthesia (i.e. spinal or general) and early PJI following THA or TKA in a large-scale observational cohort study.

Part II – Diagnosis

As mentioned earlier, diagnosing PJI can be very difficult, especially when low-virulent micro-organisms are the cause of the infection. In case of radiological signs of implant loosening or failure, distinguishing septic from the aseptic failures (in late PJI) in total joint arthroplasty is critical. Septic or aseptic causes of implant failure requires very different treatment strategies and implanting a new prosthesis (foreign body) in an infected bone and joint is detrimental.

The gold standard for diagnosing PJI are tissue cultures demonstrating growth of a specific pathogen. However, to obtain these cultures surgery is required and the cultures usually take several days to even 2 weeks to demonstrate bacterial growth. Unfortunately, there is no reliable way to determine intra-operatively that an infection is present. To overcome this dilemma, the Musculoskeletal Infection Society (MSIS) has formulated criteria for decision-making in the work-up of suspected of PJI (38). However, this work-up remains far from straightforward, mainly since there is no uniform test. Therefore, a test that can quickly and reliably distinguish between an infected or uninfected prosthesis would be invaluable. One of the relevant parameters for establishing a PJI intra-operatively according to the MSIS is the presence of higher levels of α-defensin in synovial fluid of a prosthetic joint. In an effort to accelerate intra-operative decision making between a “septic” or an “aseptic” surgical treatment a rapid test for α-defensin in the synovial fluid was developed. In **Chapter 6** the effectiveness of this test is assessed.

Part III - Treatment

If prevention fails and PJI is diagnosed accordingly, an adequate combination of surgical and antibiotic treatment is indicated. Depending on the type and timing of infection, local bone and soft tissue quality and other patient characteristics a surgical strategy can be determined. As mentioned earlier, early PJI is the most frequently encountered PJI subtype and is generally treated by means of surgical debridement, antibiotics and implant retention (DAIR). However, the efficacy of DAIR

procedures varies with reported success rates ranging between 26% to 92% (39-47). If DAIR fails or is considered unfeasible, an exchange arthroplasty either as a one- or two-stage procedure can be performed. However, these procedures may yield an even higher burden on the patient.

Empiric antibiotic treatment

Several patient or procedure related factors have been suggested that enhances a positive treatment outcome of a DAIR protocol. These factors include the absence of renal- and/or liver failure, uncemented arthroplasty, failure timely initiation of DAIR (< 3 weeks of onset of symptoms), absence of MRSA amongst the pathogens, and exchangeability of mobile parts (47-49). Some studies have suggested an association between ineffective empiric antibiotic therapy and treatment failure (50, 51). Still, optimal empiric antibiotic treatment in the context of PJI remains an underexplored aspect of its treatment in the current available literature. In **Chapter 7**, we explore the common pathogens involved in early PJI along with their antibiotic susceptibilities in order to obtain additional knowledge on the optimal empirical antibiotic therapy following DAIR.

Repeated DAIR

The aforementioned treatment success rates (which can be as low as 23%) imply that treatment failure following DAIR is not uncommon. In case of a failed (primary) DAIR procedure, the surgeon faces the dilemma to either repeat DAIR, or to proceed with a one- or two stage revision of the implant. A repeated DAIR procedure may be attempted, although this strategy is highly controversial (52). In **Chapter 8**, we assess the effectiveness of repeated DAIR procedure in case of early failure of infection control and evaluate its usefulness.

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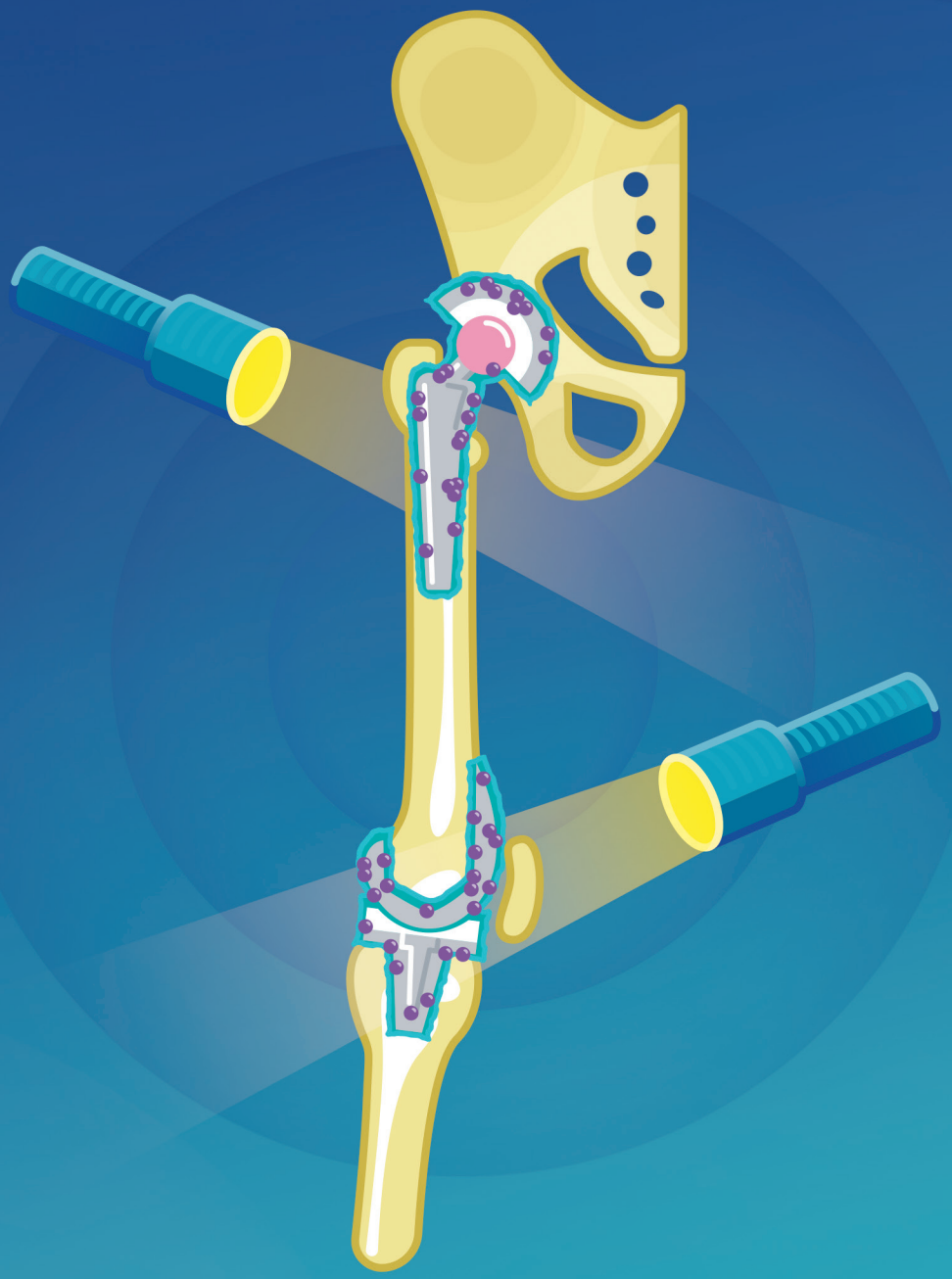

2

The incidence of mild hypothermia after total knee or hip arthroplasty: a study of 2600 patients

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ABSTRACT

Introduction: Hypothermia is associated with a higher risk of perioperative complications and occurs frequently after total joint arthroplasty (TJA).

Materials & Methods: The incidence of hypothermia following total joint arthroplasty was assessed with its risk factors and its correlation with PJI. Correlation of hypothermia with age, gender, BMI, type of arthroplasty surgery, type of anesthesia, operation time, blood loss, date of surgery and PJI was evaluated in 2600 patients.

Results: Female gender and spinal anesthesia increased the risk for hypothermia whereas an increased BMI and surgery duration correlated decreased the risk of hypothermia.

Conclusion: The incidence of hypothermia decreased over time without a correlation with PJI.

INTRODUCTION

Perioperative hypothermia can be an inadvertent effect of major arthroplasty surgery, and may result in possibly avoidable complications. In a previous study we found that the incidence of hypothermia (a core temperature below 36 ºC directly after surgery) was high, 26.7% (1). There is scarce literature on the effects of hypothermia after total knee or hip replacement. Other authors have described the negative effect of hypothermia after other types of major surgery, like abdominal surgery. They found that even mild perioperative hypothermia can increase the incidence of post-operative complications (increased mortality, sepsis, stroke, surgical site infection)(2). These effects can be considerable, a decrease of 1.9 ˚C in core temperature triples the relative risk of surgical site infection (SSI) and increases the duration of hospitalization by 20% (3). Taking protective measures to prevent the negative cascade caused by hypothermia may be particularly important in patients undergoing elective total joint arthroplasty (TJA) because patients are typically older and at risk for similar complications and infection. Periprosthetic joint infection (PJI) after primary total hip arthroplasty (THA) or total knee arthroplasty (TKA) has considerable medical consequences and a mortality rate as high as 2.5%(4).

Despite the consequences, hypothermia remains an underrated and unresolved issue. The World Health Organization 2009 guideline (among other national and international guidelines) advise perioperative normothermia to prevent unintended complications but offer no specific guidance to achieve that goal(5). Since then, several studies have attempted to establish effective methods to maintain normothermia in patients undergoing surgery in different surgical fields. A recent Cochrane review showed that most technical methods for preventing hypothermia are ineffective, only forced air warming seems to increase the patients core temperature after surgery(6).

We felt that the incidence of hypothermia in our previous study was unacceptably high and decided to do a follow-up study. We hoped to reduce the incidence of hypothermia, not by technical measures, but by raised awareness of hypothermia among the medical and nursing staff on the orthopedic ward and in the operating room (OR). In this current prospective observational cohort study we describe the long-term results, using the incidence of hypothermia as a primary outcome. We evaluated the correlation of hypothermia with both its risk factors and with PJI.

MATERIALS & METHODS

The study was approved by the institutional review board (IRB). We included all consecutive patients in our hospital undergoing elective primary unilateral total knee or total hip arthroplasty for osteoarthritis from January 2011 till December 2014. We excluded patients undergoing bilateral surgery or revision surgery. Mild hypothermia is defined as a core temperature between 35 and 36 ˚C, severe hypothermia as a core temperature below 35˚C. The core temperature was measured at the tympanic membrane (Genius™ 2) in the operation room directly after wound closure. Correlation with age, BMI, gender, type of arthroplasty surgery, type of anesthesia, operation time, blood loss, date of surgery was evaluated.

All patients were treated using the same measures to prevent hypothermia. The warming protocol was not changed during the study period. The use of a forced-air warming system (Bair-hugger©) was already implemented in our hospital, and no other warming system proved to be superior in preventing hypothermia in previous studies (7-10). Our algorithm included the following measures:

- Use forced air warming (Bair hugger) placed over the patient's chest and arms as long as the operation took, irrespective of core temperature. The Bair hugger was set on maximum temperature (42 ˚C) and adjusted for comfort of the patient
- No other warming devices were used
- Core temperature was measured before and directly after surgery in the OR
- Maintain ambient temperature between 18 and 21 ˚C
- Before and after surgery patients were covered with two double folded half cotton blankets.

We informed all medical and nursing professionals on the orthopedic ward and in the OR of the temperature measurement program. In another previous study we found that the largest decrease in body temperature occurred preoperatively on the orthopedic ward and during transport from the ward to the OR(10). Therefore, we introduced routine measurement of preoperative core temperature and started pre-warming with an electric above-patient warmer if indicated (i.e. if temperature was below 36 ˚C).

Operating technique was not changed during the years. All TKA patients were operated on using a tourniquet. All TKA's were cemented, all THA's were uncemented. General or spinal anesthesia was used in all patients depending on the patients personal favor and possible risk factors as assessed by an anesthesiologist. Reported operation time is the time between skin incision and closure of the operation wound.

Patients were diagnosed to have a PJI based on MSIS major and minor criteria (11). In case of an early infection, as defined in the IDSA guidelines (4), debridement with implant retention was performed and six cultures were obtained. Until cultures were definitive, patients were treated with intravenous antibiotics (Cefazoline). If cultures proved positive antibiotic therapy was adjusted accordingly and administered for a total of 12 weeks. If this treatment was not sufficient, a one- or two stage revision of the prosthetic joint was performed. We considered patients to have a PJI when two or more cultures were positive or when patients were treated for 12 weeks based on clinical symptoms and consensus of the orthopedic surgeon, medical microbiologist and infectiologist during our weekly meeting.

Statistical analyses were carried out using the statistical package SPSS© version 23.0. Baseline characteristics of the patients with a THA or TKA were compared using the chi square and the Mann-Whitney U-test since the Kolmogorov-Smirnov test showed that age, BMI and surgery duration were not normally distributed. The difference between mean core temperature in the hypothermia versus the normothermia group was tested with an independent sample t-test. Difference in incidence of mild hypothermia and PJI between THA and TKA was tested with chi square test. The influence of type of anesthesia, operation time, age, gender, BMI and more recent surgery date on the difference in mean core temperature in both groups was analyzed with linear regression analysis. Results with a p-value of less than 0.05 were considered to be statistically significant.

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

RESULTS

During the study period, a total of 2729 consecutive patients underwent TKA or THA. Subsequently, 129 patients were excluded because of missing temperature measurements (figure 1).

Table 1 shows the baseline characteristics of the 2600 patients in our study population, 1127 undergoing TKA and 1473 undergoing THA. There was no significant difference in type of anesthesia. However, there was a significant difference in gender, mean age, BMI and mean operation time between the two groups (table 1). 39% of the TKA patients were male versus 33.4% in the THA group. In the TKA group 74.9% received

spinal anesthesia versus 77.5% in the THA group. Mean operation time was 13 minutes longer in the TKA group than in the THA group, 59.18 vs. 46.11 minutes respectively. Furthermore, the mean BMI was 29.90 in the TKA group and 27.43 in the THA group.

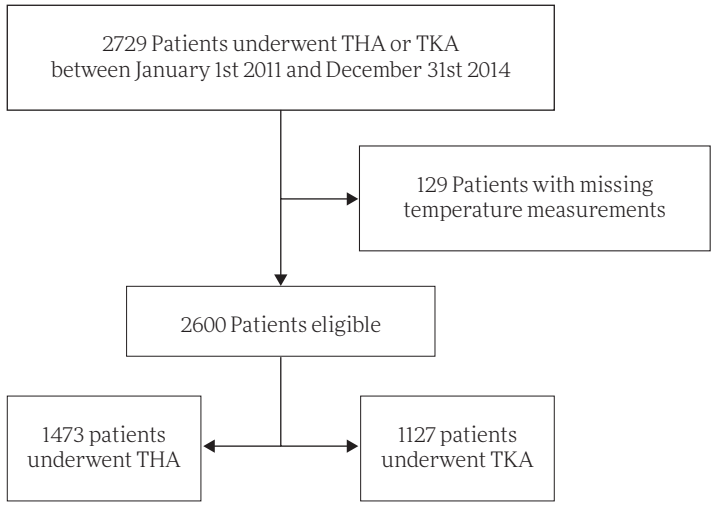

Figure 1: Flow-chart illustrating the patient inclusion process

Table 1: Baseline characteristics.

n = 2600	TKA n= 1127 (43,3%)	THA n= 1473 (56,7%)	p-value
Gender M : F (%)	440 : 687 (39% : 61%)	492 : 981 (33.4% : 66.6%)	0.003
Mean Age (years)	67.57 [38-92]	69.34 [32-92]	0.000
Type of Anesthesia S : G	839 : 281 (74.9% : 25,1%)	1132 : 328 (77.5% : 22.5%)	0.120
Mean Operation time (min)	67.55 [25-131]	69.32 [18-200]	0.000
Mean Body Mass Index	29.97 [18-48]	27.46 [15-47]	0.000

Percentages are given between brackets, ranges are given between square brackets. S=spinal anesthesia; G=general anesthesia.

Our primary outcome was an overall incidence of 11.7% of mild hypothermia. The incidence of mild hypothermia in the TKA group was 1.8% lower than in the THA group (10.7 vs. 12.5% respectively). This difference was not significant, p=0.172. We did not observe moderate or severe hypothermia. Mean core temperature directly after arthroplasty surgery was 36.5 °C in both groups (SD=0.5149). In the TKA group the standard deviation was 0.0144 and in the THA group 0.0140. There was no significant statistical difference (p=0.521). A chi-square test showed a significant difference between the incidences of hypothermia between the years 2011 and 2012 (p=0.000), 2012 and 2013 (p=0.042), but not between the years 2013 and 2014. A linear regression analysis shows a negative linear relationship between gender and core temperature (p=0.000) and type of anesthesia and core temperature (p=0.033). A positive linear relationship was shown between core temperature and BMI (p=0.000), female gender (p=0.000) and the date of surgery (p=0.000). Both patient age (p=0.062) and blood loss (in the THA group, all TKA were placed using a tourniquet) were not related with core temperature (p=0.221). Please refer to table 2 and 3 for more details.

Table 2: Mean postoperative body temperature and incidence of hypothermia and infections.

n = 2600	Total (n=2600)	TKA (n=1127)	THA (n=1473)	p-value
% < 36 °C	305 (11.7 %)	121 (10.7 %)	184 (12.5 %)	0.168
Mean temp	36,5 °C	36.5 °C	36.5 °C	0.990
% Infections	46 (1.8%)	17 (1.5%)	29 (2.0%)	0.378

Table 3: Multivariate linear regression analysis model of the relation between the type of anesthesia, BMI, duration of surgery, gender, arthroplasty type (hip or knee), age and the postoperative core temperature.

n = 2600	B	95% CI	P
Gender	-0.103	-0.148 – -0.059	0.000
Type of Anesthesia	-0.054	-0.105 – -0.004	0.035
Body Mass Index	0.008	0.004 – 0.013	0.000
Duration of surgery	0.001	0.000 – 0.003	0.110
Date of surgery	1.975E-9	0.000 – 0.000	0.000
Age	-0.002	-0.004 – 0.000	0.062
Arthroplasty type	-0.018	-0.065 – 0.029	0.452

B = regression coefficient; 95% CI = 95% confidence interval for B; P = significance.

Forty-six patients (1.8%) were diagnosed with PJI. In the TKA group the incidence of PJI was 1.5% PJI, in the THA group the incidence was 1.9%. This difference was non-significant (p=0.378). The incidence of PJI was 1.0% in hypothermic patients versus 1.9% in normothermic patients. This yields a non-significant (p=0.27) relative risk ratio of 0.52. In the THA group, in the normothermic subgroup the incidence of PJI was 2.2%, the incidence of PJI in the hypothermic subgroup was 0%. This difference was significant, p=0.041. After TKA, the incidence of PJI was 1.4% in the normothermic subgroup and 2.5% in the hypothermic subgroup. This difference was not significant (p=0.354).

DISCUSSION

This study indicates that the incidence of inadvertent hypothermia can be reduced. We found that the incidence of mild hypothermia decreased over the study period, with a ceiling effect after two years. We suspect that increased awareness among the staff on the ward and the OR combined with pre-operative heating may be an explanation for the decline in the incidence of hypothermia. We found an overall incidence of 11.7% in primary total knee or hip arthroplasty. This is much lower than the incidence we found in our previous 2013 study, which was 26.7%.

A higher BMI is positively correlated with a higher post-operative core temperature. Females appear to be at greater risk of developing hypothermia after TJA. Spinal anesthesia seems negatively correlated with post-operative body temperature. A previous study did not find significant differences between spinal or general anesthesia, but this could be due to the relative smaller sample sizes in those studies compared to this study (12). Spinal anesthesia is believed to lead to hypothermia because of a decreased shivering- and vasoconstriction threshold and vasodilatation in the lower extremities (12). Our data indicates spinal anesthesia may result in greater decrease in body temperature than general anesthesia, but show no difference in mean post-operative core temperature after TKA or THA.

Mild hypothermia was not associated with a higher incidence of PJI. This is contradictory to the findings in other fields of surgery(2, 13). The difference might be explained by the severity of hypothermia. Perhaps only severe hypothermia leads to an increased risk of infection. Another possible explanation is that in patients with a high risk of PJI more attention is given to the prevention of hypothermia. A third possibility is that other factors are more important in the development of a PJI. A higher BMI is correlated to a higher core temperature but also leads to a higher chance of a PJI (14). The international consensus group on PJI has identified certain host

(or patient) factors for PJI, which include male gender, previous surgery, uncontrolled diabetes mellitus, malnutrition, morbid obesity, active liver or renal disease, smoking or excessive alcohol consumption, intravenous drug abuse, recent hospitalization, active infection, inflammatory arthropathy and severe immunodeficiency (11). However, it could very well be that we have establish a false-negative result. The latter might be due to the low incidence of PJI in general. Even though we present a relatively large cohort of patients for a single-center study, our study is underpowered to identify a significant difference of 0.05.

Previous studies have tried to establish effective methods to prevent inadvertent hypothermia. These methods mainly consisted of equipment to either warm the patient actively or to passively keep the patient warm during surgery with intensified temperature monitoring. Large scale results show that only forced-air warming seems effective in preventing inadvertent hypothermia and that the use of thermal insulation methods are not effective in maintaining normothermia(6, 7, 9). Combined strategies, including preoperative commencement of warming devices, are more effective then isolated measures in vulnerable groups (higher age or longer duration of surgery)(8). One study showed that an underbody warming system could reduce the incidence of hypothermia in laparoscopic gastrointestinal surgery (15). The latter might be useful as an additional method to warm patients during TJA, but to date no studies have been published on its use in orthopedic surgery. It remains doubtful if it has additional value, since arthroplasty procedures require less operating time then most laparoscopic procedures.

We conclude that creating awareness among the medical and nursing staff can result in a lower incidence of hypothermia in patients undergoing TKA or THA. This could be an important tool in the reduction of post-operative adverse events. Further studies assessing larger cohorts of patients are required to establish a correlation between hypothermia and PJI.

Conflict of interest and funding

All authors, their immediate families, and any research foundation with which they are affiliated did not receive any financial payments or other benefits from any commercial entity related to the subject of this article.

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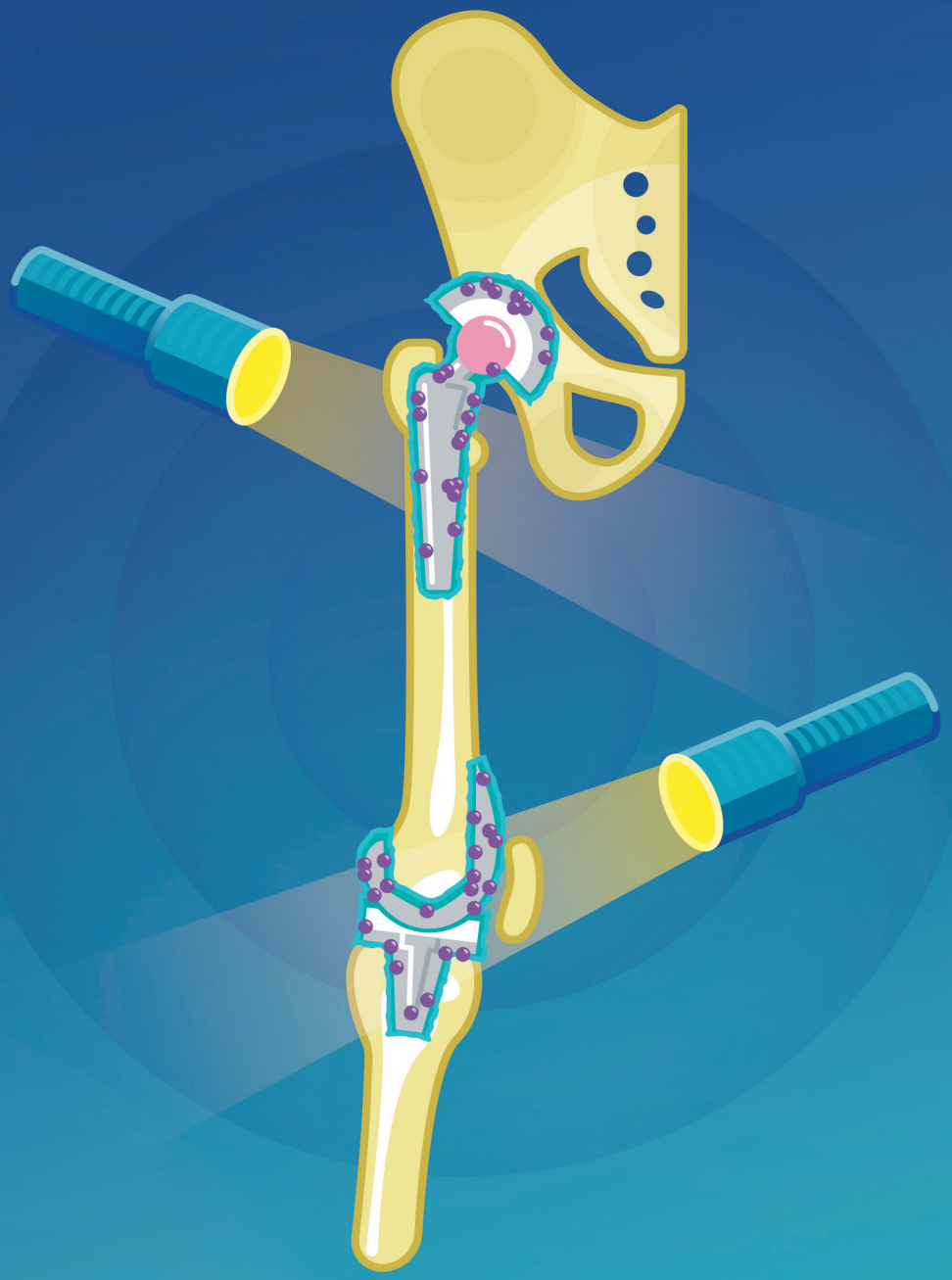

3

Preoperative Staphylococcus aureus screening and eradication

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ABSTRACT

Introduction: Pre-operative nasal *Staphylococcus aureus* (SA) screening and eradication reduces surgical site infections (SSI) but remains controversial regarding early periprosthetic joint infection (PJI). This study aims to assess the effect of preoperative nasal SA screening and eradication on the incidence of early PJI in general and SA induced early PJI.

Materials & Methods: All primary total hip arthroplasties (THA) and total knee arthroplasties (TKA) performed from January 2006 through April 2018 were retrospectively reviewed for the incidence of early PJI. Demographic parameters, risk factors for PJI (ASA classification, Body Mass Index, smoking status, and diabetes mellitus) and implant types were collected. A preoperative screening and eradication protocol for nasal colonization of *S. aureus* was introduced in October 2010. The incidence of early PJI was compared before and after the implementation of the latter. Missing data were imputed via multiple imputation by chained equations. Inverse probability weighting was used to account for differences between patients in both groups. Weighted univariable logistic regression was used to evaluate the incidence of early PJI for both groups.

Results: 10,486 THAs and TKAs were performed in the research period. After exclusion, a cohort of 5,499 screened cases and 3,563 non-screened cases were available for analysis. Overall, no significant reduction in early PJI was found in the screened group (OR: 0.78; 95%CI: 0.55 – 1.11; p = 0.18). However, the incidence of SA induced PJI was significantly reduced (OR: 0.58; 95%CI: 0.36 – 0.92; p=0.02) in the screened group.

Conclusion: A pre-operative nasal SA screening and eradication protocol did not significantly reduce the overall incidence of early PJI after THA or TKA. However, a decreased incidence of SA induced early PJI was established. These findings can help to establish better consensus around the value of these screening protocols where reduction of PJI can be weighed against overall (cost) effectiveness.

INTRODUCTION

Periprosthetic joint infection (PJI) following surgical site infection (SSI) remains a serious complication in total joint arthroplasty (TJA). It is the most common indication for revision total knee arthroplasty (TKA), and the third most common reason for revision total hip arthroplasty (THA) (1). The reported incidence of early PJI for both THA and TKA ranges from 0.2% to 2.2% (2, 3). Several modifiable risk factors are known to predispose to the development of PJI. These include poor glycaemic control, obesity, malnutrition, smoking along with perioperative variables, such as timely and appropriate dosage of prophylactic antibiotics, skin preparation with chlorohexidine-based solution, and irrigation with dilute betadine at the end of the operation (4). In addition, preoperative Staphylococcus aureus (SA) screening and eradication treatment is suggested to decreased rates of PJI (4).

SA has previously been identified as the most common micro-organism causing SSI and nasal carriage of SA appears to be a major risk factor for the development of SSI(5). This raised the idea that eradication of nasal SA may reduce the incidence of SSI. It has been shown that a 5-day course of intranasal mupirocin is indeed effective in eradicating nasal SA (6). In a randomized controlled trial, Bode et al. confirmed the efficacy of a SA screening and eradication protocol to reduce the incidence of SSIs following a variety of surgical procedures (7). Subsequently, several studies also suggested a reduction of SSI after TJA after the implementation of comparable pre-operative nasal SA screening and eradication protocols (6, 8-10). However, there is no consensus whether these protocols are also capable to reduce the actual number of true prosthetic joint infections.

As such, the available evidence regarding the effectiveness of these widely introduced and costly screening and eradication protocols remains controversial. This controversy is also substantiated by the fact that up to 20% of patients may remain colonized despite completing this eradication protocol (11), SA carriage is underestimated with standard culturing techniques (12) and that nasal staphylococcus colonization is intermittent in many patients and as such may be missed at the time of screening(13). This dilemma has been recognized in a recent international consensus meeting from a panel of PJI content experts where preoperative SA screening and decolonization was categorized as lacking evidence for its effectiveness on the prevention of PJI and urged for better studies focusing on this topic (14).

Therefore, the aims of this study were to assess the effectiveness of a preoperative SA screening and eradication protocol in 1) reducing the incidence of early overall PJI, and 2) the reduction in SA induced early PJI in patients following elective primary TKA and THA in a cohort of roughly 10.000 patients.

MATERIALS & METHODS

Patients who underwent elective total hip (THA) or knee arthroplasty (TKA) from January 2006 to May 2018 were identified using our computerized database. Unicompartmental or patellofemoral knee replacements (less invasive surgery and relatively uncommon procedure) were excluded along with metal-on-metal THA (potential bias from early adverse reaction to metal debris). Further exclusion criteria consisted of prior osteosynthesis on the affected joint, proximal femoral fracture as the indication for primary THA as well as any kind of arthroplasty revision surgery (Figure 1). Patient charts were reviewed for the presence of the most common risk factors for PJI (4). Data on Body Mass Index (BMI), smoking status and diabetes were retrieved together with the corresponding American Society of Anesthesiologists (ASA) classification at the time of the THA or TKA procedure.

In October 2010, a protocol was introduced to screen all patients undergoing elective primary THA or TKA for nasal colonization of SA before surgery. After the indication for either THA or TKA, patients were instructed by a nurse practitioner how to take a culture from the nares, and how to apply the decolonization treatment if necessary. According to protocol, the swab had to be obtained within 14 days prior to surgery.

Cultures were obtained from the nares using Eswab medium (Copan, Menen, Belgium). Cultures were inoculated on a blood agar plate for 48 hours incubation at 35°C. SA isolates were determined using MALDI-TOF (15), resistance to antimicrobial agents including mupirocin was assessed using Vitek® (Biomérieux, Salt Lake City, USA).

The nurse practitioner was informed about all cultures in which SA was isolated. Subsequently, the nurse practitioner informed the patient in case of positive culture results and instructed those patients how to apply mupirocin ointment (20 mg/g) in the nares 3 times a day and once daily wash their body and hair with chlorhexidine soap (chlorhexidine 40 mg/ml). The eradication treatment started three days before surgery and was continued for five days.

At the time of surgery all patients received prophylactic administration of cefazolin (2000 mg) within an hour before surgery, followed by 3 administrations of 1000 mg of cefazolin every 6 hours. No change in surgical technique for either THA or TKA occurred during the study interval. For THA, poor bone quality or age >75 years were indications for a cemented (Exeter®; Stryker Howmedica) implant. Otherwise uncemented implants (Zweymuller®; Zimmer up to 2014 and from then on CLS Spotorno®/Allofit; Zimmer) were used. All TKA patients underwent cemented TKA (LCS; Johnson&Johnson) by means of medial parapatellar arthrotomy. No uncemented TKAs were performed. Antibiotics loaded bone cement (Palacos® R+G; Heraeus,

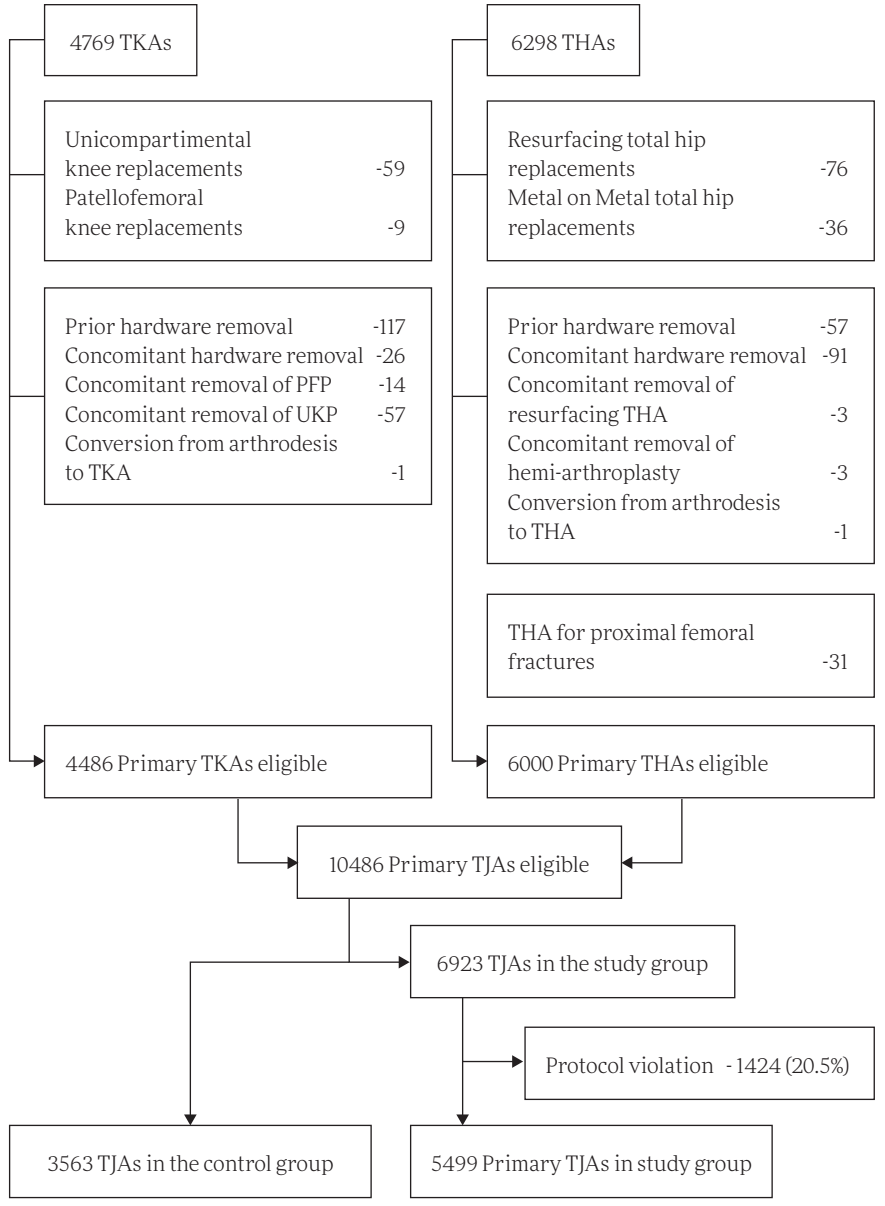

Figure 1: Flowchart illustrating the patient inclusion process.

THA: Total hip arthroplasty, TKA: Total knee arthroplasty, TJA: Total joint arthroplasty.
*Some patients were screened >14 days prior to surgery, or not screened at all due to divergent reasons.

containing 0.75g of gentamycin base sulfate per 61.2g of powder) was used in both TKA and THA. All arthroplasty procedures were performed in the same hospital in operating theatres allocated to orthopaedic implant procedures under comparable conditions and protocols. Prior to discharge patients were closely monitored for signs of potential post-operative infection. Following discharge, all patients were subjected to protocolized surveillance of infection in the outpatient clinic for at least 3 months after surgery. In case of prolonged wound drainage (>10 days), suspected (superficial) SSI or superficial wound breakdown, surgical debridement using antibiotics and implant retention (DAIR) was performed. During every DAIR procedure multiple intra-articular periprosthetic tissue samples were obtained and cultured. In this study we only focused on early PJI, established within 3 months of surgery.

Subsequently all included patients' charts were retrospectively reviewed for re-admittance, infection or repeated surgery within 3 months following the primary total hip or knee arthroplasty. All data on possible PJI were critically assessed against the 2018 definition of PJI (figure 2) which served as the definition of PJI for this study (16).

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	Score	Decision
Preoperative Diagnosis	Serum	Elevated CRP *or* D-Dimer	2	≥6 Infected 2-5 Possibly Infected [a] 0-1 Not Infected
		Elevated ESR	1	
	Synovial	Elevated synovial *WBC count or LE*	3	
		Positive alpha-defensin	3	
		Elevated synovial PMN (%)	2	
		Elevated synovial CRP	1	

	Inconclusive pre-op score *or* dry tap [a]	Score	Decision
Intraoperative Diagnosis	Preoperative score	-	≥6 Infected 4-5 Inconclusive [b] ≤3 Not Infected
	Positive histology	3	
	Positive purulence	3	
	Single positive culture	2	

Figure 2: New scoring-based definition for periprosthetic joint infection (PJI). Proceed with caution in: adverse local tissue reaction, crystal deposition disease, slow growing organisms.

CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; LE, leukocyte esterase; PMN, polymorphonuclear; WBC, white blood cell. [a]For patients with inconclusive minor criteria, operative criteria can also be used to fulfill definition for PJI. [b]Consider further molecular diagnostics such as next-generation sequencing (from Parvizi, 2018) (16).

The study protocol was approved by our institutional ethical review board (no. 2018-1275).

Statistical methods

Multiple imputation by chained equations procedures were used to impute missing values (17). We generated 30 imputed datasets, as current guidance recommends that one imputation should be performed per percent of incomplete observations (18). ASA-classification, diabetes, BMI, and smoking had 6.1%, 11.1%, 26.5%, and 26.7% missing values respectively (Table 1).

The difference regarding the incidence of early PJI between the control group and screening group might be biased by confounding baseline characteristics. To address systematic differences between screening and control/no-screening group, we used inverse probability of treatment weighting (IPTW) analyses. IPTW, a form of propensity score analysis, uses weighting by the inverse of the propensity score to reduce imbalance in measured confounders between treatment groups (19). The propensity score was defined as the probability of being screened or not, dependent on a case's recorded baseline characteristics. Propensity scores were estimated independently for each imputed dataset, using a logistic regression model with the group (control or screened) as the dependent variable in relation to the following baseline characteristics: age, gender, ASA-classification, BMI, smoking, diabetes, and type of arthroplasty surgery. The selection of which variables to include in our analyses in order to minimize bias was done using directed acyclic graphs based on the approaches described by Shrier and Pearl (20, 21). The propensity scores were used to calculate each patient's inverse probability of being in the screening or in the control group. Post-weighting balance in covariates between screening and control groups was evaluated both graphically and descriptively using standardized differences. A standardized difference of less than 10% indicates an appropriate balance (22). Mean standardized mean differences with their range across the 30 multiple imputed datasets are provided in Table 2. Figure 3 displays the balance summarized across imputations.

On each of the 30 imputed datasets, a weighted univariable logistic regression with a robust variance estimator was used to determine the effect of screening on early PJI (23). The resulting estimates were pooled using Rubin's rule (24). Subsequent subgroup analysis regarding the type of arthroplasty (THA or TKA) was performed. Statistical analyses were performed using R 3.6.3 (R Foundation for Statistical Computing, Vienna, Austria) with packages 'mice', 'WeightIt', 'cobalt', and 'survey'.

RESULTS

From January 2006 through April 2018, 10,486 primary unilateral total hip and knee arthroplasties were performed, of which 6,923 were performed after the implementation of the pre-operative SA screening and eradication protocol (Figure 1). The control group thus consisted of 3,563 patients. Demographic data are displayed in Table 1.

For the screening group the nasal cultures had to be obtained within 14 days prior to surgery according to the protocol. Throughout the entire course of the screening period the upper limit of 14 days appeared to have been slightly exceeded in a rather large number of cases, which resulted in the exclusion of another 1,424 patients (20.5%) from this protocol violation. Eventually, 5,499 patients in the screening group were successfully screened within 14 days prior to surgery according to the protocol (Figure 1). Thus, the entire cohort consisted of 9,062 patients, 5,499 from the screening group and 3,563 from the control group.

In the screening group, 1,469 (26.7%) of 5,499 cases screened positive for nasal carriage of SA. Three (0.1%) cases were confirmed as a carrier of nasal MRSA.

For the entire cohort, in 135 out of 9,062 (1.5%) patients an early PJI was identified. In the THA and TKA subgroups, early PJI was identified in 90 out of 5,163 (1.7%) and 45 out of 3,899 (1.2%) respectively. The unadjusted percentages of infection in the screened subgroups and the control subgroups were 2.0% (control) and 1.7% (screened) for THA, and 1.7% (control) and 0.9% (screened) for TKA.

For each imputed dataset, inverse probability weighting was used to account for differences between patients who were screened and those who were not. Mean standardized mean differences with their range across the 30 multiple imputed datasets are provided in Table 2. Figure 3 displays the balance summarized across imputations before and after IPTW. Pooled weighted univariable regression analysis demonstrated no significant differences regarding the risk of early PJI between the screened group (1.3%) and the control group (1.7%) (OR: 0.78 95%CI: 0.55 – 1.11; p = 0.18). Subsequent subgroup analysis addressing the risk of early PJI in THA and TKA (screening vs. control) patients separately showed odds ratios (0.95; 95% CI 0.61 - 1.45; p = 0.79 and 0.55; 95% CI 0.30 – 1.00; p = 0.05, respectively).

Table 1: Patient characteristics and missing data among the screened and control groups from the unadjusted cohort. Percentages are displayed as valid (calculated through discarding missing data, except for the ASA classifications) percentages.

	Total (n = 9062)	**Missings, n (%)**	**Control group (n = 3563)**	**Missings, n (%)**	**Screened group (n = 5499)**	**Missings, (n%)**
Age (mean (SD))	69.12 (9.87)	0 (0%)	69.81 (10.08)	0 (0%)	68.67 (9.71)	0 (0%)
Male gender (n (%))	2994 (33.0%)	0 (0%)	1074 (30.1%)	0 (0%)	1920 (34.9%)	0 (0%)
ASA		550 (6.1%)		537 (15.1%)		13 (0.2%)
ASA 1 (n (%))	1300 (14.3%)	-	465 (13.1%)	-	835 (15.2%)	-
ASA 2 (n (%))	6007 (66.3%)	-	2181 (61.2%)	-	3826 (69.6%)	-
ASA 3 (n (%))	1172 (12.9%)	-	371 (10.4%)	-	801 (14.6%)	-
ASA 4 (n (%))	33 (0.4%)	-	9 (0.3%)	-	24 (0.4%)	-
BMI (mean (SD)	28.8 (4.38)	2400 (26.5%)	28.45 (4.86)	1772 (49.7%)	28.93 (4.81)	628 (11.4%)
Active smoker (n (%))	819 (9.0%)	2424 (26.7%)	267 (7.5%)	1546 (43.4%)	552 (10%)	878 (16.0%)
Diabetes Mellitus (n (%))	717 (7.9%)	1007 (11.1%)	333 (9.3%)	943 (26.5%)	384 (7%)	64 (1.2%)
TKA (n (%))	3899 (43.0%)	0 (0%)	1396 (39.2%)	0 (0%)	2503 (45.5%)	0 (0%)

SD: Standard Deviation; n: number of patients; BMI: Body Mass Index; TKA: Total Knee Arthroplasty; ASA American Society of Anesthesiologists score; PJI: Periprosthetic Joint Infection.

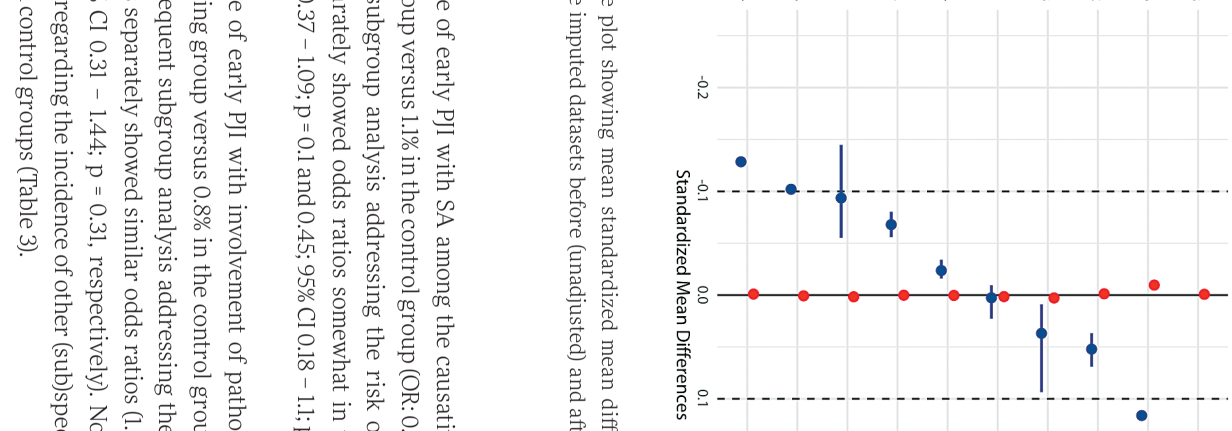

Figure 3: Love plot showing mean standardized mean differences with their range across the 30 multiple imputed datasets before (unadjusted) and after inverse probability weighting (adjusted).

The incidence of early PJI with SA among the causative pathogens was 0.6% in the screening group versus 1.1% in the control group (OR: 0.58; 95% CI: 0.36 – 0.92; p=0.02). Subsequent subgroup analysis addressing the risk of early PJI in THA and TKA patients separately showed odds ratios somewhat in favour of the TKA subgroup (0.63; 95% CI 0.37 – 1.09; p = 0.1 and 0.45; 95% CI 0.18 – 1.1; p = 0.08, respectively).

The incidence of early PJI with involvement of pathogens other than SA was 0.9% in the screening group versus 0.8% in the control group (OR: 1.05; 95% CI: 0.65 – 1.7l; p=0.82). Subsequent subgroup analysis addressing the risk of early PJI in THA and TKA patients separately showed similar odds ratios (1.43; 95% CI 0.76 – 2.68; p = 0.25 and 0.67; 95% CI 0.31 – 1.44; p = 0.31, respectively). No significant differences were encountered regarding the incidence of other (sub)species of pathogens between the screened and control groups (Table 3).

Table 2: Balance across multiple imputations before and after inverse probability weighting.

	Balance across imputations before IPW			Balance cross imputations after IPWi		
	Control Group	Screened group	SMD, mean (range)	Control group	Screened group	SMD, mean (range)
Age (mean (SD))	69.81 (10.08)	68.67 (9.71)	0.1161 (0.1161 - 0.1161)	68.99 (10.40)	69.08 (9.64)	-0.0096 (-0.0110 - -0.0085)
Male gender (%)	30.14%	34.92%	-0.1020 (-0.1020 - -0.1020)	33.06%	33.03%	0.0007 (-0.0005 - 0.0024)
ASA						
ASA 1 (%)	15.32%	15.23%	0.0026 (-0.0096 - 0.0227)	15.38%	15.33%	0.0014 (0.0005 - 0.0033)
ASA 2 (%)	72.11%	69.74%	0.0521 (0.0366 - 0.0689)	70.57%	70.63%	-0.0013 (-0.0032 - 0.0001)
ASA 3 (%)	12.28%	14.59%	-0.0679 (-0.0803 - -0.0559)	13.66%	13.66%	0.000 (-0.0029 - 0.0021)
ASA 4 (%)	0.29%	0.44%	-0.0237 (-0.0340 - -0.0161)	0.39%	0.38%	0.0003 (-0.0020 - 0.0026)
BMI (mean (SD)	28.45 (4.83)	28.90 (4.83)	-0.0936 (-0.1448 - -0.0551)	28.73 (4.92)	28.72 (4.80)	0.0016 (-0.0002 - 0.0032)
Active smoker (%)	13.29%	12.06%	0.0368 (0.0089 - 0.0935)	12.66%	12.57%	0.0028 (0.0007 - 0.0042)
Diabetes Mellitus (%)	12.49%	7.16%	0.1798 (0.1659 - 0.1943)	9.20%	9.23%	-0.0008 (-0.0011 - -0.0005)
TKA (%)	39.18%	45.52%	-0.1285 (-0.1285 - -0.1285)	42.97%	43.02%	-0.0010 (-0.0024 - -0.0003)

Balance between groups is presented as mean standardized mean differences with the corresponding minimum and maximum standardized mean differences across the 30 multiple imputed datasets. Patient characteristics are presented as pooled mean (SD) (continuous variables) or as pooled percentages (binary/categorical variables) across multiple imputations. IPW: Inverse Probability Weighting; SMD: Standardized Mean Difference; BMI: Body Mass Index; TKA: Total Knee Arthroplasty; ASA American Society of Anesthesiologists score.

Table 3: Adjusted incidence of overall early periprosthetic joint infections and the incidences of (sub)species of causative pathogens in each group with the corresponding odds ratios, 95% confidence intervals and p-values.

	Control group	Screened group	OR (95% CI)	p-value
All PJI	1.71%	1.35%	0.78 (0.55 - 1.11)	0.17
S. aureus related infections	1.09%	0.63%	0.58 (0.36 - 0.92)	0.02
CNS related infections	0.25%	0.35%	1.37 (0.61 - 3.07)	0.44
Enteric gram-negative related infections	0.32%	0.31%	0.99 (0.45 - 2.18)	0.99
Streptococcus related infections	0.21%	0.20%	0.95 (0.36 - 2.49)	0.91
Enterococcus related infections	0.07%	0.15%	2.14 (0.45 - 10.10)	0.33
Pseudomonas related infections	0.00%	0.03%	2.99 (0.14 - 63.56)	0.48
Corynebacterium related infections	0.06%	0.12%	3.65 (0.45 - 29.84)	0.23
Other pathogens related infections	0.80%	0.85%	1.06 (0.65 - 1.71)	0.82

CNS: Coagulase Negative Staphylococcus; OR: Odds Ratio; CI: Confidence Interval.

DISCUSSION

Nasal SA carriage is a widely recognized risk factor for the development of SA related infections(5). However, despite relatively strong evidence for the effectiveness of SA screening and eradication in the prevention of SSI in general, the effectiveness of comparable protocols in the prevention of PJI in general remains to be elucidated(16).

This study revealed no significant overall reduction (OR: 0.78; 95%CI: 0.55 – 1.11; p = 0.18) in early PJI in primary THA and TKA following the implementation of a pre-operative SA screening and eradication protocol in a consecutive series of more than 9,000 patients. However, for the incidence of SA induced early PJI a significant decrease (OR: 0.58; 95%CI: 0.36 – 0.92; p=0.02) was found.

These findings are important and may further elucidate on the recent consensus meeting where the effectiveness of screening and eradication of SA was considered to lack evidence in the context of arthroplasty and PJI. In the paucity of literature so far there are only a few studies available on the effect of the implementation of nasal SA screening and subsequent decolonization on the incidence of PJI(10, 25).

Schweizer et al. also evaluated whether the implementation of a bundled intervention of SA screening and subsequent eradication treatment and protocolized preoperative antibiotics was associated with a lower risk of SA SSIs(10). The rates of complex SA

SSIs decreased significantly after hip or knee arthroplasties (difference per 10,000 operations, -17 [95%CI, -39 to 0]; RR, 0.48 [95%CI, 0.29 to 0.80]), whereas the rates by any pathogen (mean rate per 10,000 operations, 68 for the preintervention period versus 45 for the intervention period; RR, 0.67 [95%CI, 0.44 to 1.00]) did not decrease significantly. The authors conclude, similarly to our study, that a significant reduction in SA PJI did not result in a significant decrease in the overall incidence of PJI. The relatively large patient number with real world data in a relatively short time-interval are important strengths of the study by Schweizer et al., however limitations also apply. First, the reported adherence to the screening bundle was only 83% and both complete and incomplete bundle adherence was accepted. Secondly, partly due to the multicentre setting, the surveillance of the presence of a complex SSI was less well defined and controlled. Finally, from the pragmatic clinical set-up, there may have been a relatively large potential for bias from confounding factors. The latter is illustrated by a plethora of missing values on important risk factors for PJI such as BMI and smoking. In addition, several PJIs may have been missed since patients with complex SSIs after joint replacements were assumed to be seen by their local surgeons for diagnosis and treatment.

In contrast to both our study and the study by Schweizer et al., Jeans et al. did report on a significant overall reduction in PJI following THA after the introduction of preoperative SA screening and eradication, whereas after TKA no effect on reduction of PJI could be confirmed(25). In spite of the fact that this study also evaluated a large cohort of THA and TKA patients', a clear definition of when a patient was classified as having a PJI was lacking and the percentage of nasal SA carriers in their study population was not reported. Both these factors may have influenced their results. In addition, the authors report on a baseline infection rate of 3% in their THA group prior to the introduction of a screening and eradication protocol. This rather high incidence of PJI in the control group may allow larger margins for improvement in time which could have caused other factors then solely the introduction of screening to have played a role in reaching the encountered significant decrease in overall PJI incidence.

Strengths of our study include a large patient cohort, the absence of (other) major changes regarding infection prevention over the course of the study period and a representative control group. Furthermore, through the application of inverse probability weighting utilizing propensity scores based on BMI, smoking status, diabetes, ASA-classification, age, type of arthroplasty and gender the potential allocation bias was reduced.

Limitations also apply mainly from this study's retrospective design. For example, patients suffering from (early) PJI may have sought care at other institutions despite of our local follow-up protocol, this cannot be ruled out entirely. However, since early postoperative follow-up was protocolized this confounding bias is unlikely to have occurred. The latter was confirmed by data obtained from the Dutch national joint registry claiming that from the implants (THAs and TKAs) which were placed in our institution from 2007-2018, 126 early (<1 year) revisions were performed, out of which only 2 for THA and 2 for TKA were performed elsewhere.

In addition, eradication treatment compliance with the SA screening may be a concern. However, eradication treatment compliance remains a confounder which is very difficult to control and to quantify. Therefore, these results could be considered an appropriate reflection of daily practice. In fact, this limitation accounts for all studies available in the literature on this topic. In our opinion treatment compliance simply remains a concern or weakness with the screening protocols themselves which should be taken into account in weighing the balance of potential benefit of introduction.

Finally, due to the long timeframe of this study, other factors than solely the implementation of the SA screening and eradication protocol may have contributed to our results. For instance, the implementation of the use of tranexamic acid, the use of Spica bandages after THA, the use of Aquacell® wound dressings and changing brands of implanted THAs over the course of the study period were encountered and may have influenced these results. However, since these interventions are not specifically aimed at the prevention of infection and not related to infection whatsoever, we argue that their influence would have been minimal.

In summary, this study demonstrates a significant decrease in SA induced PJI without a significant decrease in the overall incidence of PJI after the implementation of a SA screening and eradication protocol in a large number of patients whilst adequately correcting for confounding risk factors for PJI. As such, it appears that more consensus has been achieved on the effect of SA screening and eradication on the incidence of PJI. It is beyond the scope of this study to make a recommendation for or against these SA screening and eradication protocols. Statistical significance has to be balanced against the clinical relevance of the absolute numbers in PJI reduction obtained and costs. Numbers needed to screen are large with respect to the achieved decrease, especially for PJI in general. In addition, it should be noted that in spite of adequate screening and eradicating SA carriers there still is concern with this technique around the fact that a substantial percentage of carriers is not identified using these screening techniques and that patients may remain colonized

despite eradication treatment(11, 12). Perhaps an alternative diagnostic means for screening (e.g. Polymerase Chain Reaction (PCR)) yields better results (12). As an alternative, universal decolonization (treating all patient with nasal mupirocin, without screening) has also been suggested as more effective at reducing early PJI and more cost-efficient when compared to a screening and selective decolonization protocol (26). However, a serious concern with universal decolonization is the potential development of widespread mupirocin resistance by the overtreatment of 74% patients.

In conclusion, this study does not identify a significantly reduced incidence of early PJI following THA and TKA after the implementation of pre-operative nasal SA screening and eradication despite a large number of included patients. However, a significant reduction of SA induced early PJI was found. These results raise further evidence to balance the true clinical value of widespread implementation of SA screening and decolonization in elective TJA especially when considering the expensive and labor-intensive nature of these protocols.

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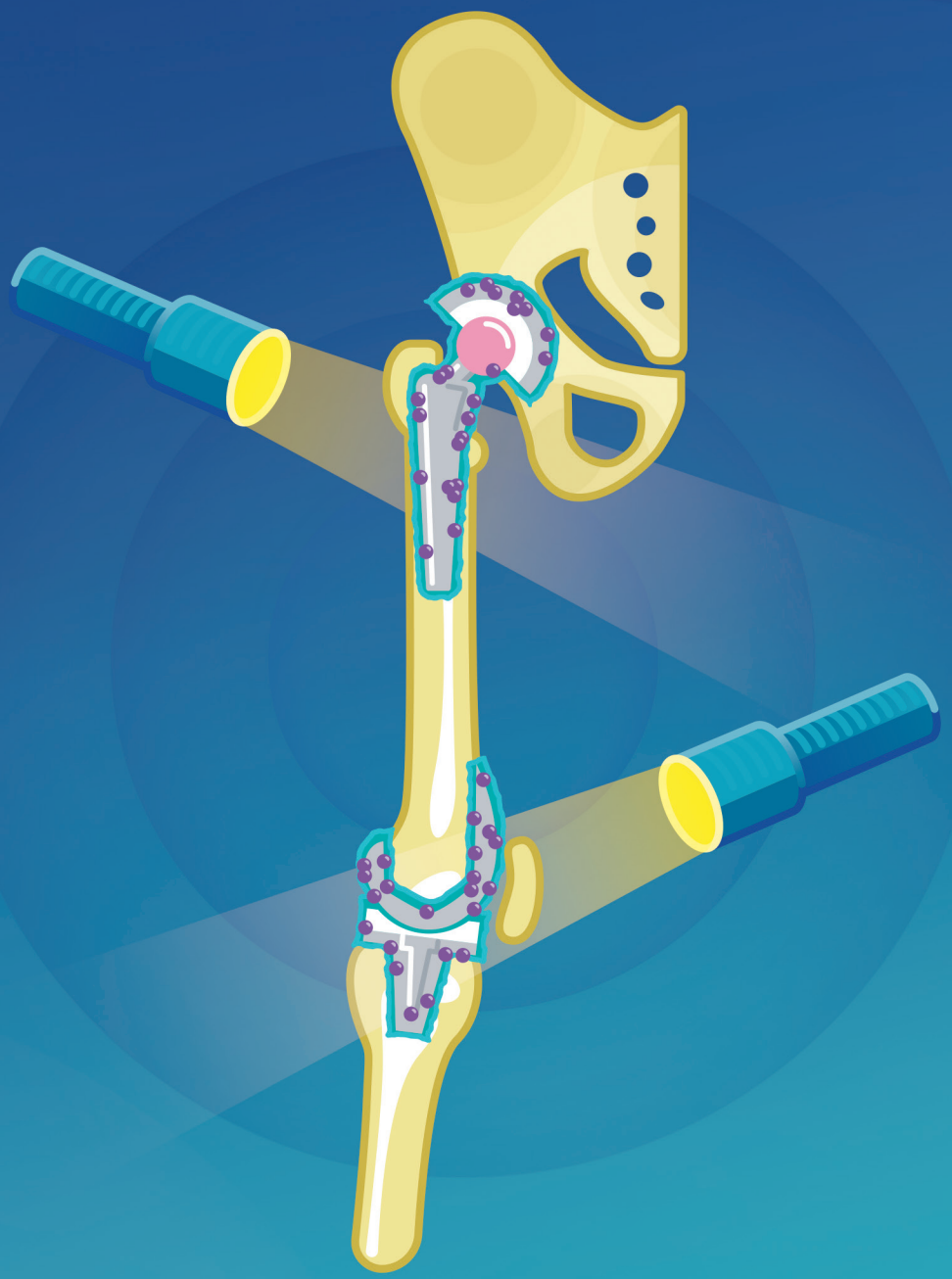

4

High incidence of periprosthetic joint infection following total hip arthroplasty with concomitant or previous hardware removal

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ABSTRACT

Introduction: Hardware removal preceding total hip arthroplasty may increase the risk of prosthetic joint infection (PJI). Whether hardware removal and total hip arthroplasty (THA) should be performed as a single- or two-stage procedure remains controversial. In this comparative retrospective study the incidence of PJI following either single- or two-stage THA after hardware removal was assessed in a consecutive series.

Materials & Methods: All patients that underwent hardware removal followed by THA from January 2006 up until March 2018 were retrospectively reviewed and checked for the occurrence of early PJI. Recognised risk factors for PJI at the time of surgery were evaluated.

Results: 145 patients underwent THA and hardware removal (52 two-stage surgery and 93 single-stage surgery). There were no significant differences between both groups regarding pre-operative hemoglobulin levels, time interval between internal fixation and THA, cement use in THA, BMI and ASA-classification. Overall the incidence of early PJI was 6.9 percent. The incidence of PJI was 8.6 percent in the single-stage group versus 3.8 percent in the two-stage group (p=0.315).

Conclusion: Irrespective of single- or two stage procedures, a high incidence of PJI was encountered. Despite non-significance, a trend towards a higher proportion of patients developing PJI after single-stage surgery was encountered. We recommend a two-stage surgical procedure regarding hardware removal and THA in patients that are expected to tolerate this surgical strategy. When considering a one-stage procedure, it should preceded by a thorough pre-operative work-up including joint aspiration and determination of inflammatory parameters. Multiple tissue samples should be obtained during hardware removal in either one- or two-stage procedures since the risk for development of PJI should not be underestimated.

INTRODUCTION

The incidence of proximal femoral fractures has increased over the last decade and continues to rise to an expected amount of 21 million people with this injury in the next 4 decades (1). Primary (hemi-) arthroplasty for femoral neck fractures is recommended in elderly patients and for displaced fractures (2). However, internal fixation for intertrochanteric fractures or fracture of the femoral neck in younger patients remains a reliable treatment option. Still, up to 30% of internal fixations may fail requiring the need for secondary or salvage total hip arthroplasty (THA) (3). Clinical outcomes and complication rates following secondary THA after internal fixation of proximal femoral fractures tend to be inferior compared to primary THA for the treatment of proximal femoral fractures (3-6).

Periprosthetic joint infection (PJI) is one of the most serious complications of THA and accounts for up to 15% of failed THA (7). The reported incidence of PJI following primary elective THA ranges from 0.2% to 2.2% (8). A recent systematic review reported on an increased risk for PJI following THA after internal fixation of a proximal femoral fracture compared to primary THA for hip fractures (3). Since then, new studies have again addressed the outcomes of salvage THA finding no increased risk for PJI (6, 9). Thus, there still appears to be a lack of consensus in the literature on a potential increased risk of PJI in case of concomitant implant removal at time of THA. In addition there is no consensus whether a single step procedure, combining implant removal and consecutive hip arthroplasty, or a separated two stage procedure should be advocated. Proponents of a 2-stage procedure with hardware removal and actual arthroplasty as separate surgical procedure mainly do so based on a study that identified 53% bacterial contamination rate at the time of removal of screws, plates or nails used for internal fixation (10).

At the other end of the spectrum Klatte et al. performed a retrospective study to specifically address the safety of 1-stage secondary THA regarding infection and found it to be a safe procedure without a single case of PJI (11). From these controversies in literature, the aim of this retrospective study was to further elucidate on (1) the incidence of early PJI following salvage THA following hardware removal, and to (2) compare the incidences of early PJI following either single-stage or two-stage THA with implant removal.

MATERIALS & METHODS

We retrospectively reviewed all patients that underwent secondary THA following hardware removal from January 2006 and up until March 2018. A total of 6275 THA patients were retrieved from our electronic database and subsequently the database was filtered for patients where hardware removal was also performed prior to or at time of the THA. A chart review was performed on the included patients and patients with hardware removal beside the involved hip were excluded. The indication for and the type of osteosynthesis was recorded together with comorbidities according to the American Society of Anaesthesiologists' (ASA) classification, Body Mass Index (BMI), pre-operative hemoglobulin levels, and surgery duration. In case intra-operative tissue cultures were taken at time of hardware removal this was registered. The choice for a single or two-stage approach was solely based on the surgeon's or the patient's preferences after informed consent.

In all patients a posterolateral approach was used both for hardware removal and for THA. Poor bone quality as quantified by DEXA or age >75 years were indications for cemented THA (Exeter; Stryker). Otherwise an uncemented THA (Zweymuller; Zimmer up to and including 2013 and from then on CLS Spotorno/Allofit; Zimmer) was used. The used bone cement (Palacos G; Heraeus) contained gentamycin. All patients received perioperative antibiotic prophylaxis with 2 grams of Cefazolin within 1 hour of the start of surgery and 3 grams postoperatively over the course of 24 hours. Physical therapy was commenced on the day of surgery when possible.

Early PJI (<3 months postoperatively) was suspected by means of increasing C-reactive protein levels, persistent wound leakage or fever with the surgical site as suspected focus of infection and the absence of other foci. In these cases debridement and implant retention (DAIR) was performed and a minimum of 6 intraoperative tissue cultures were obtained. The diagnosis of PJI was confirmed by the presence of 2 or more positive intra-operative tissue cultures with an identical pathogen taken during initial DAIR for suspected PJI according to the Musculoskeletal infection society (MSIS) criteria (6). Responsible pathogens were recorded.

Data was analysed using SPSS© version 23. Chi-square and Student t-tests were used. P-values < 0.05 were considered statistically significant. A waiver was obtained for the execution of this study by the local institution's review committee.

RESULTS

In total, 148 patients were identified where a THA was combined with hardware removal, either in a one or a two stage procedure. One patient was excluded for undergoing hemiarthroplasty instead of THA and 2 patients were excluded for receiving a THA on the contralateral side.

Thus, 90 women and 55 men were included. In 93 patients (mean age 66, range 41-98) a one stage procedure was performed, whereas in 52 patients (mean age 62, range 23-83) the THA was preceded by hardware removal at an earlier stage. The mean time interval between internal fixation and subsequent THA was 4 years and 8 months (range 2 months to 49 years. There were no significant differences between both groups in pre-operative hemoglobulin levels, time interval between internal fixation, used fixation devices, cemented or uncemented THA, ASA classification and BMI. Operation time ($p<0.001$), patient age ($p=0.038$), and patient age ($p=0.04$) differences were significant. Also, non-union and cut-out of implants as an indication for THA were significantly more prevalent in the one-stage group whereas hip dysplasia as the indication for internal fixation (after osteotomy) was significantly more prevalent in the two-stage group. Tables 1 and 2 provide a complete overview of patient characteristics for both study subgroups.

Overall, 11 patients underwent DAIR for suspected post-operative surgical site infection (SSI). Among these patients, 10 were confirmed as PJI by means of 2 or more positive intra-operative tissue cultures demonstrating identical pathogens. 1 Patient was revised for instability due to malpositioning 3 weeks after THA implantation, 5 out of 6 tissue cultures taken during revision surgery demonstrated *S. aureus* and was therefore also diagnosed as early PJI. This yields an overall incidence of early PJI was 6.9%. In the single-stage and two-stage procedures the incidence of early PJI was 8.6% and 3.8% respectively ($p=0.234$). In 4 cases, polymicrobial PJI was identified. All but a single patient were treated successfully by means of DAIR (and in one case revision and irrigation) followed by antibiotic treatment. The single patient in which DAIR followed by antibiotic treatment proved unsuccessful eventually underwent two-stage revision. All cultured pathogens are listed in table 3.

Table 1: Overview of patient characteristics and statistical differences between the single- and two-stage surgery groups.

	1-Stage Surgery		2-Stage Surgery		
	Number	**Percentage**	**Number**	**Percentage**	**P-Value**
Indication for primary surgery					
Femoral neck fracture	59	63.4%	33	63.5%	0.572
Pertrochanteric fracture	24	25.8%	13	25.0%	0.540
Subtrochanteric fracture	6	6.5%	3	5.8%	0.588
Acetabular fracture	1	1.1%	0	0%	0.641
Epiphysiolysis	2	2.2%	0	0%	0.410
Hip dysplasia	0	0%	3	5.8%	0.044
Pathological fracture	1	1.1%	0	0%	0.641
Fixation device					
Screws	13	14.0%	7	13.5 %	0.572
Intramedullary nail	27	29.0%	16	30.8%	0.485
Dynamic hip screw	52	55.9%	25	48.1%	0.232
Angled blade plate	1	1.1%	2	3.8%	0.292
Fixation plate & screws	0	0%	2	3.8%	0.127
Indication for secondary THA					
Osteoarthritis	18	19.4%	15	28.8%	0.136
New fracture	3	3.3%	6	11.5%	0.054
Femoral head necrosis	17	18.3%	10	19.2%	0.527
Non-union	21	22.6%	4	7.7%	0.017
Mal-union	18	19.4%	15	28.8%	0.136
Cut out of implants	16	17.2%	2	3.8%	0.014
Type of THA					
Cemented	38	41%	17	33%	0.214
Uncemented	55	59%	35	67%	0.214
ASA-Classification					
1	9	9.7%	10	19.2%	0.086
2	55	59.1%	27	51.9%	0.252
3	17	18.3%	11	21.2%	0.416
4	10	10.8%	4	7.7%	0.389
Unknown	2	2.2%	0	0%	0.410
BMI					
Underweight (<18.5)	3	3.2%	3	5.8%	0.369
Normal weight (18.5-24.9)	38	40.9%	22	42.3%	0.501
Overweight (25-29.9)	37	39.8%	16	30.8%	0.184
Obese (30-39.9)	11	11.8%	10	19.2%	0.410
Morbidly obese (>39.9)	2	2.2%	0	0%	-
Unknown	2	2.2%	1	1.9%	0.708
Gender					
Male	30	32.3%	25	48.1%	0.045
Female	63	67.7%	27	51.9%	0.045

P-values were calculated using the chi-square test. Significant values are underlined.

Table 2: Overview of patient characteristics and statistical differences between the single- and two-stage surgery groups with the corresponding units between brackets.

	1-Stage surgery		2-Stage surgery		
	Mean	**Range**	**Mean**	**Range**	**p-value**
Pre-operative hemoglobulin level (mmol/l)	8.4	5.8-10.8	8.6	6.4-11.1	0.219
Surgery duration (min)	91	43-190	70	32-146	0.000
Time from osteosynthesis to THA (months)	56	0-422	33	2-587	0.095
Age (years)	66	41-98	62	23-83	0.038

P-values were calculated using the independent samples students' t-test. Significant values are underlined.

Table 3: Isolated pathogens in patients that underwent DAIR for suspected acute PJI with their corresponding incidence.

Isolated pathogen	**Incidence (n)**	**Percentage (%)**
Staphylococcus Epidermidis	3	27%
Pseudomonas Aerigunosa	2	18%
Corynebacterium Species	2	18%
Enterococcus Faecalis	2	18%
Staphylococcus Aureus	1	9%
Beta-hemolytic Streptococcus (Group C)	1	9%
Enterobacter Cloacae	1	9%
Staphylococcus Lungdunensis	1	9%
Total isolated pathogens	11	100%

DISCUSSION

PJI remains a serious complication following THA. Due to the increasing number of patients requiring salvage THA after previous internal fixation of a proximal femoral fracture it is important to establish consensus on the potentially higher risk of PJI and whether a one or two stage procedure should be advocated (1, 10, 11). To date, reports on the incidence of PJI following secondary THA after earlier internal fixation vary from 0% to 7.5% indicating the lack of consensus regarding the subject.

Overall, the incidence of PJI in this study was 6.9% which is substantially higher than the commonly reported overall incidence rate of 0.2% to 2.2% regarding PJI after elective THA. These results support the notion of an increased risk of PJI following hardware removal which has been incidentally reported in previous literature (12, 13). This however, contradicts the findings of several other studies that identified no increased risk of PJI following THA after hardware removal (6, 9, 11). This apparent discrepancy could be attributed to differences in patient population or selection since this study is conducted in a large general teaching hospital and not in an academic or highly specialized orthopaedic clinic. The latter is supported by the fact that the proportion of patients with ASA classification 3 and 4 is substantially higher (29% vs. 15%) when compared to the study performed by Klatte et al (11). Furthermore, Tetsunaga et al. did not include ASA 4 patients, and Hernandez et al. did not report on ASA classifications at all (6, 9). Furthermore, none of these studies used well-defined criteria for PJI which makes interpretation of these results difficult and might entail a potential risk of negative bias in detecting PJI. However, the latter is also problematic regarding studies of older date addressing this subject. Mainly since the MSIS criteria have been formulated in 2011, all prior studies use differing criteria for PJI or "deep infection". All in all, we argue that the risk of PJI may very well be increased when performing secondary THA following previous or concomitant hardware removal in the context of a large general teaching hospital.

The choice for either a concomitant or separated procedure regarding hardware removal and THA remains subject to debate and evidence to support either strategy is lacking. Klatte et al. specifically addressed the safety of single stage procedures regarding hardware removal and THA. They concluded there is no increased risk for PJI in single-stage hardware removal and THA with a PJI incidence of 0% (11), but it was not compared to two-stage procedures. In contrast to these results, this study demonstrates a 8.6% incidence of early PJI regarding single-stage hardware removal and THA. In two-stage procedures, this incidence was 3.8%. The difference between these percentages was not statistically significant. Two statistically significant differences regarding known risk factors for PJI were present between both groups:

surgery duration and patient age. Surgery duration is expected to be higher in the single-stage surgery group since it requires additional surgical proceedings. Whether it is responsible for the increased incidence of PJI in the single-stage group is uncertain. Perhaps bacterial contamination of the primary orthopaedic fixation device plays a role in these cases as suggested by Moussa et al (10). As previously mentioned, mean patient age is slightly higher in the one-stage group which could theoretically increase the risk for PJI. However, we argue this small difference of 4 years is hardly clinically relevant.

Furthermore, the percentage of patients undergoing single-stage secondary THA for non-union or cut out of implants is significantly higher compared to the two-stage surgery group. The latter may suggest that non-union or cut-out of implants predispose to early PJI following THA. Perhaps some of these non-unions are due to low-grade infection of the fixation device (14). In addition to these previous considerations, all bone cement used in cemented THA contained gentamycin. Therefore, the cement may serve as an extra protective measure for PJI and serve as a source of bias. However, since the proportions of cemented and cementless THA are comparable between both groups, we argue this does not hold true. On top of that, the proportion of cemented THA is higher in the one-stage group, which is contradictory to the higher incidence of PJI in that group.

Despite the fact that the difference between both subgroups is not statistically significant, it is proportionally large. Perhaps a two-stage procedure may indeed reduce the risk of PJI but to establish this possible correlation, comparative studies assessing larger cohorts are required.

Previous studies have addressed the possible high incidence of bacterial contamination of orthopaedic implants by means of positive intra-operative cultures and their relevance (10, 11). Some institutions prefer to perform their secondary arthroplasties in two stages based on the this notion on possible contamination of the fixation device. Moussa et al. argued that positive intra-operative cultures should be disregarded in the absence of clinical signs of infection (10). However, positive tissue cultures taken during hardware removal preceding THA may yet have to be taken into serious consideration and followed by adequate antibiotic treatment before THA since the results by Klatte et al. suggest the incidence of bacterial contamination is not as high as previously suggested.

The major limitation of this study is its retrospective design for apparent reasons. Also, the included number of patients is too low to establish a significant difference on the incidence of PJI between one-stage and two-stage procedures. Furthermore, the

patients were included over a long period of time leading to a varied cohort. The latter makes our conclusions (which are not statistically significant) less reliable. Despite a thorough search of the patient files some missing values were left untraceable. However, these limitations might be considered as an appropriate reflection of daily practice in a large general teaching hospital.

In conclusion we encountered a high incidence of PJI after salvage THA following implant removal after earlier internal fixation. This incidence supports the few available studies in the higher range of reported PJI. The trend towards a patient population with comorbidities and a relatively high ASA classification may have played a role in the discrepancy with literature reporting lower incidences of PJI. In addition, other studies may have had a negative selection bias whereas in our study all PJIs were classified according to the latest MSIS criteria and proven by intraoperative tissue cultures. Despite the absence of a significant difference there was a clear trend towards a higher incidence of PJI in the single-stage subgroup. The percentage of positive intra-operative tissue cultures at the time of implant removal was low, suggesting a low rate of bacterial contamination from the index surgery. Based on our findings we recommend that the incidence of PJI following salvage THA after internal fixation should not be underestimated. From the results of this study we decided to consider these procedures as revisions for suspected infection. Prior to subsequent THA we advise a thorough work-up including joint aspiration for culturing and to evaluate blood serum infection parameters. A two-stage procedure is advocated whilst obtaining 6 tissue cultures at the time of implant removal. In case these cultures prove positive adequate prolonged antibiotic treatment for either osteomyelitis or PJI should be initiated. When considering a single-stage procedure, additional diagnostic tests like the intra-operative use of the Synovasure® lateral flow test might be of additional value for excluding pre-existent infection.

For the future, further well-designed studies comparing either one- or two-stage strategies should be performed to further establish the optimal surgical strategy in this challenging subgroup of patients.

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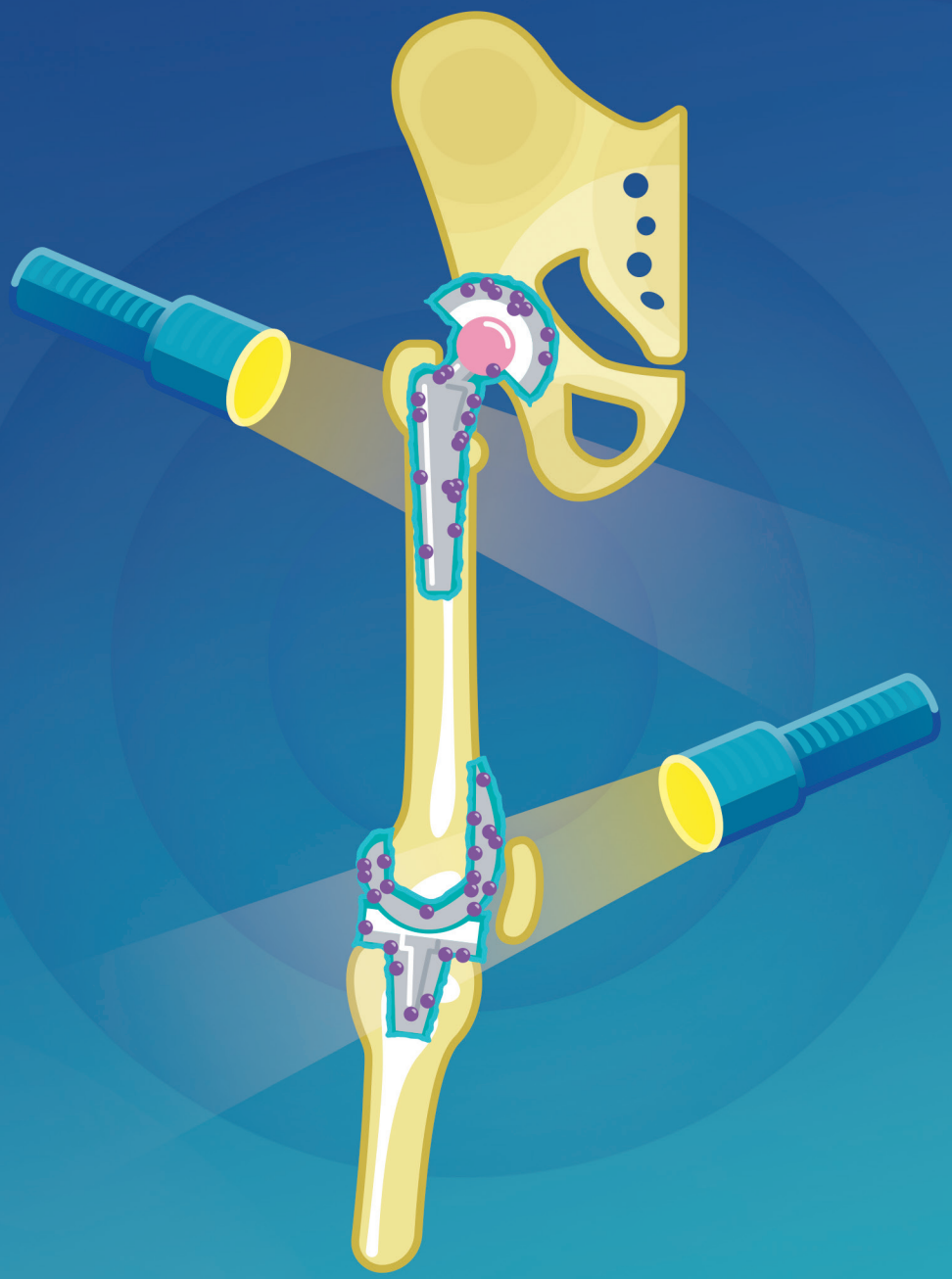

5

General anesthesia might be associated with early periprosthetic joint infection: an observational study of 3909 arthroplasties

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ABSTRACT

Introduction: Periprosthetic joint infection (PJI) remains a devastating complication following total knee or total hip arthroplasty (TKA/THA). Nowadays, many studies focus on preventive strategies regarding PJI, however, the potential role of anesthesia in the development of PJI remains unclear.

Materials & Methods: All consecutive patients undergoing elective primary unilateral TKA or THA from January 2014 through December 2017 were included. Exclusion criteria included femoral fractures as the indication for surgery and previously performed osteosynthesis or hardware removal on the affected joint. Age, BMI, sex, ASA classification, type of arthroplasty surgery, type of anesthesia, duration of surgery, smoking status and intra-operative hypothermia were recorded. Propensity score matched univariable logistic regression analysis was used to control for allocation bias.

Results: 3909 procedures consisting of 54% THAs and 46% TKAs were available for analysis. 42% arthroplasties were performed under general anesthesia and 58% under spinal anesthesia. Early PJIs were observed in 1.7% of the general anesthesia group and in 0.8% in the spinal anesthesia group. The multivariable logistic regression model demonstrated an odds ratio for PJI of 2.0 (95% CI 1.0 - 3.7) after general anesthesia relative to the propensity score matched patients who received spinal anesthesia.

Conclusion: These results suggest a potential association between general anesthesia and early PJI. Future research using large-scale data is required to further elucidate this clinically relevant association.

INTRODUCTION

Periprosthetic joint infection (PJI) is responsible for up to 25% of failed TKA and 15% of failed THA (1, 2). Despite the increasing awareness of certain patient characteristics that influences the risk of PJI (3), the role of procedure related factors, such as the type of anesthesia, remains to be elucidated (4). Remarkably, the notion that anesthesia may influence the immune response has been suggested as early as 1903 (5). In the late 70s and 80s several reviews identified the ability of anesthetic agents to influence a wide variety of specific and non-specific host defenses (5). However, the clinical relevance and the exact role of anesthesia in the pathogenesis of postoperative infections remains unclear (5, 6).

Several studies have suggested spinal anesthesia to reduce the risk for SSI when compared to general anesthesia in THA and TKA (7, 8), however, other studies found no clear difference between both types of anesthesia and their influence on surgical site infection (SSI) (9-11). Still, a recent systematic review suggested that regional anesthesia seems to decrease the risk of SSI when compared to general anesthesia (12). Despite several clues pointing to general anesthesia predisposing to infection, no studies assessing the role of anesthesia during THA and TKA with well-defined definitions of PJI have been performed.

Therefore, we investigated the relationship between type of anesthesia (i.e. spinal or general) and PJI following THA or TKA in a large-scale observational cohort study.

MATERIALS & METHODS

All consecutive patients undergoing elective primary unilateral TKA or THA for osteoarthritis in a single general teaching hospital from January 2014 through December 2017 were retrieved from the hospital's prospective database. Subsequent exclusion criteria were proximal femoral fracture or acetabular fracture as the indication for primary surgery and concomitant or previous hardware removal on the affected joint. Data was recorded regarding the patient's age, sex, ASA classification, BMI, smoking behavior, type of arthroplasty surgery, type of anesthesia, surgery duration, intra-operative hypothermia, and length of stay.

Over the course of the study period a similar surgical technique was used, and no changes to the surgery protocol were implemented. Patients received prophylactic administration of 2 grams cefazolin 15 to 60 minutes prior to skin incision or tourniquet inflation, followed by 3 administrations of 1 gram after surgery with an

8-hour interval. All THAs were performed by, or under direct supervision of, 1 of 7 hip surgeons. Accordingly, all TKAs were performed by 1 of 4 knee surgeons. Several residents or trainees participated in most surgeries. All TKA patients underwent surgery while using a tourniquet which was inflated 15 to 60 minutes after infusion of the prophylactic cefazoline and deflated after applying a pressure bandage over the affected knee. Only patients with primary implant models and no revision models were included. All TKAs were cemented and performed using a medial parapatellar arthrotomy. THA was performed using a posterolateral approach. Both cemented and uncemented THA were performed with a patient age cut-off point below 75 years for uncemented THA. The bone cement (Palacos® R+G; Heraeus) used in both TKA and THA contained 0.75 grams of gentamicin per 61.2 grams of powder. The decision to apply either general- or spinal anesthesia during the arthroplasty was at 1 of the senior anesthesiologist's discretion and based on the patients' personal preference. Patients were extensively informed on both general- and spinal anesthesia, after which they could indicate their preference. To correct for potential allocation bias introduced through this selection procedure, propensity score-based matching of cases was performed (please refer to statistics for further information)

Surgical duration was defined as the time between skin incision and closure. The core temperature was measured at the tympanic membrane (Genius™ 2; Medtronic) in the operation room directly after wound closure.

Prior to discharge patients were closely monitored for signs of potential post-operative infection. Following discharge, all patients were subjected to protocolized surveillance of infection in the outpatient clinic for at least 3 months after surgery. In case of prolonged wound drainage (>10 days), suspected (superficial) surgical site infection (SSI) or superficial wound breakdown, surgical debridement, with antibiotics and implant retention (DAIR) was performed. During DAIR, 6 periprosthetic tissue biopsies were always obtained and subsequently cultured. Superficial SSI was defined according to the Infectious Centers of Disease Control (CDC) guidelines with the presence of: (1) purulent incisional drainage, (2) positive culture of aseptically obtained fluid or tissue from the superficial wound, (3) local signs and symptoms of pain or tenderness, swelling, and erythema after the incision is opened by the surgeon (unless culture negative), or (4) diagnosis of SSI by the attending surgeon or physician based on their experience and expert opinion (13).
Until final cultures results were obtained up to 10 days after DAIR, patients were treated with intravenous antibiotics (flucloxacillin, 6g/day via continuous intravenous infusion).

PJI was diagnosed according to the major Musculoskeletal Infection Society (MSIS) criteria by means of 2 or more tissue cultures demonstrating growth of an identical pathogen (14). If PJI was diagnosed, antibiotic therapy was adjusted accordingly in consultation with the attending microbiologist.

The primary outcome of this study was the incidence of PJI within 3 months of surgery.

Statistics

Multiple imputation by chained equations procedures were used for missing values to increase precision and to avoid bias (15). We generated 25 independent imputed datasets, as current guidance recommends that 1 imputation should be performed per percent of incomplete observations (16). Smoking behavior and hypothermia had 4.1% and 24% missing values, respectively, whereas other variables had less than 0.1% missing values (Table 1).

Table 1: Distribution of patient characteristics and missing data among the general anesthesia and spinal anesthesia groups.

	Spinal anesthesia (n = 2279)	**Missing data (%)**	**General anesthesia (n = 1630)**	**Missing data (%)**	**Cumulative missing data (%)**
Age (mean (SD))	70 (9.5)	0	67 (10)	0	0
Male sex (n (%))	789 (34.6%)	0	597 (36.6%)	0	0
BMI (mean (SD))	28.71 (4.70)	0	29.7 (5.17)	2 (0.1%)	2 (0.0%)
ASA 1 (n (%))	348 (15.3%)	0	221 (13.6%)	1 (0.1%)	1 (0.0%)
ASA 2 (n (%))	1614 (70.8%)	0	1049 (64.4%)	1 (0.1%)	1 (0.0%)
ASA 3 (n (%))	306 (13.4%)	0	344 (21.1%)	1 (0.1%)	1 (0.0%)
ASA 4 (n (%))	11 (0.5%)	0	15 (0.9%)	1 (0.1%)	1 (0.0%)
Active smoker (n (%))	231 (10.6)	101 (4.4%)	223 (14.2)	61 (3.7%)	162 (4.1%)
TKA (n (%))	1082 (47.5%)	0	716 (43.9%)	0	0
2014 (n (%))	674 (29.6)	0	286 (17.5)	0	0
2015 (n (%))	591 (25.9)	0	391 (24.0)	0	0
2016 (n (%))	488 (21.4)	0	518 (31.8)	0	0
2017 (n (%))	526 (23.1)	0	435 (26.7)	0	0
Surgery duration	59 (16)	0	62 (16)	0	0
Hypothermia	87 (5.6%)	724 (31.8%)	54 (3.8%)	223 (13.7%)	947 (24.2%)
PJI (n (%))	19 (0.8%)	0	28 (1.7%)	0	0

Percentages are displayed as valid (calculated through discarding missing data) percentages. BMI: Body Mass Index, TKA: Total Knee Arthroplasty, PJI: Periprosthetic Joint Infection.

A difference for the risk for early PJI between cases that received spinal- and those that received general anesthesia might be biased by confounding. A particularly important type of confounding in this case is "confounding by indication", which occurs when the clinical indication for selecting a particular intervention also affects the outcome. For example, patients with more severe comorbidities (e.g. CVD) are more likely to receive general anesthesia, but they are also more likely to develop early PJI. Another type of confounding is "confounding by association", which occurs when both exposure (i.e. type of anesthesia) and outcome (i.e. early PJI) are associated with a third variable. For example, BMI is associated both with type of anesthesia and with increasing risk of early PJI.

In order to adjust for potential confounding baseline characteristics, we matched patients based on their propensity scores (17). The propensity score was defined as the probability of receiving general anesthesia during TJA dependent on a case's recorded baseline characteristics. Propensity scores were estimated independently for each imputed dataset, using a logistic regression model with type of anesthesia as the dependent variable in relation to the following baseline characteristics: age, sex, BMI, ASA-classification, smoking status, THA or TKA surgery, and year of surgery. The selection of which variables to include in our analyses in order to minimize bias was done using directed acyclic graphs based on the approaches described by Shrier and Pearl (18, 19). A 1:1 optimal matching algorithm was applied without replacement to match exposed and non-exposed cases on their corresponding propensity scores within a caliper of 0.2 standard deviation of the logit of the propensity score (20). A 1:1 matching on propensity score was used as it has been shown that it tends to minimize bias compared to many-to-1 matching on propensity score (21). The balance between both groups after matching was checked graphically and descriptively. A standardized difference of less than 10% indicates an appropriate balance (20). Standardized differences (difference in means divided by the pooled standard deviation) of the baseline characteristics for a randomly selected matched dataset are provided in Table 2.

On each of the 25 imputed and propensity score matched datasets, a univariable logistic regression analysis with PJI within 3 months after surgery as the dependent variable and type of anesthesia as independent variable was performed. The resulting estimates were pooled using Rubin's rule (17). Statistical analyses were performed using R 3.5.2 (R Foundation for Statistical Computing, Vienna, Austria).

Table 2: Distribution of number and corresponding proportions or means and corresponding standard deviation of patient characteristics and comorbidities among the general anesthesia and spinal anesthesia groups before and after matching based on propensity scores for a randomly selected imputation set.

	Before matching			After matching		
	Spinal anesthesia (n = 2279)	**General anesthesia (n = 1630)**	**Standardized difference**	**Spinal anesthesia (n = 1630)**	**General anesthesia (n = 1630)**	**Standardized difference**
Age (mean (SD))	70 (9.5)	67 (10.1)	-0.25	68 (9.7)	67 (10.1)	-0.08
Male gender (n (%)	789 (34.6%)	597 (36.6%)	0.04	607 (37.2)	597 (36.6)	0.0
BMI (mean (SD))	28.71 (4.7)	29.7 (5.2)	0.13	29.14 (4.9)	29.37 (5.2)	0.05
ASA 1 (n (%)	348 (15.3%)	221 (13.6%)	-0.05	236 (14.5)	221 (13.6)	-0.03
ASA 2 (n (%)	1614 (70.8%)	1049 (64.4%)	-0.14	1105 (67.8)	1049 (64.4)	-0.06
ASA 3 (n (%)	306 (13.4%)	344 (21.1%)	0.19	279 (17.1)	344 (21.1)	0.09
ASA 4 (n (%)	11 (0.5%)	15 (0.9%)	0.05	10 (0.6)	15 (0.9)	0.03
Active smoker (n (%)	231 (10.6)	223 (14.2)	0.11	201 (12.3)	232 (14.2)	0.05
TKA (n (%)	1082 (47.5%)	716 (43.9%)	-0.07	735 (45.1)	716 (43.9)	-0.02
2014 (n (%)	674 (29.6)	286 (17.5)	-0.32	298 (18.3)	286 (17.5)	-0.02
2015 (n (%)	591 (25.9)	391 (24.0)	-0.05	425 (26.1)	391 (24.0)	-0.06
2016 (n (%)	488 (21.4)	518 (31.8)	0.22	465 (28.5)	518 (31.8)	0.07
2017 (n (%)	526 (23.1)	435 (26.7)	0.08	442 (27.1)	435 (26.7)	0.0

BMI: Body Mass Index, TKA: Total Knee Arthroplasty.

Ethics, funding and potential conflicts of interest

The local institutional review board approved this study (study number: 2018-1276). All authors, their immediate families, and any research foundation with which they are affiliated did not receive any financial payments or other benefits from any commercial entity related to the subject of this article.

RESULTS

Between January 1, 2014 and December 31, 2017, 4026 primary unilateral total hip and knee arthroplasties were performed. 58 THAs and 59 TKAs were excluded due to previous or concomitant hardware removal, leaving 3909 joints consisting of 2111 (54%) hips and 1798 (46%) knees available for analysis.

Among all eligible patients, 1630 (42%) arthroplasties were performed under general anesthesia and 2279 (58%) arthroplasties were performed under spinal anesthesia. Apart from the DAIR procedures, 17 cases underwent revision surgery within 3 months of primary TJA (Table 3). None of these cases were eventually diagnosed with early PJI.

Table 3: Number of patients requiring revision surgery within 3 months of index surgery.

	n
Recurrent dislocation	7
Periprosthetic fracture	8
Spinout of insert	1
Femoral stem subsidence	1
Total	17

n: number of cases.

47 early PJIs were diagnosed through 2 or more positive intra-operative tissue cultures, obtained during DAIR, demonstrating an identical pathogen. 28 (1.7%) PJIs occurred in the general anesthesia group and 19 (0.8%) in the spinal anesthesia group.

The covariate balance before and after propensity-score based matching is displayed in Figure 1 and Table 2. In the 1630 patients who received general anesthesia 28 (1.7%) PJIs occurred, while in the 1630 matched participants who received spinal anesthesia, 13-15 (0.8-0.9%) PJIs occurred, depending on imputation set.

The odds ratio for early PJI was estimated to be 2.0 (95%CI 1.0 - 3.7) for patients who received general anesthesia compared to matched patients who received spinal anesthesia.

Although no longer statistically significant, subsequent subgroup analysis addressing THA and TKA separately showed similar odds ratios (THA: 2.1 (95%CI 0.99 - 4.6) & TKA: 2.0 (95%CI 0.53 - 7.9).

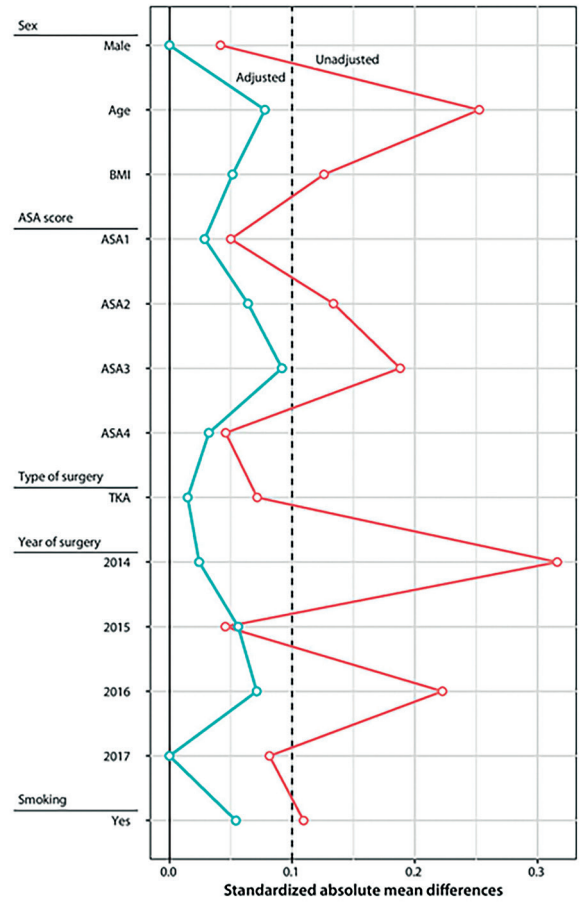

Figure 1: Figure illustrating the covariate balance before (unadjusted) and after (adjusted) propensity score matching.

Standardized differences less than 10% (dashed line) indicate an appropriate (20).

DISCUSSION

Over the past decade, several studies have suggested that spinal anesthesia decreases the risk for SSI after TJA when compared to general anesthesia (7, 8). However, this remains debated since many conflicting results have been reported and there is a paucity of high quality studies using objective criteria for SSI (9-11). The distinction between (superficial) SSI and early PJI in orthopedic surgery is far from straightforward yet clinically important. In 1999, the Centers for Disease Control (CDC) formulated definitions for superficial-, deep incisional- and organ/space SSI (22). However, there are no procedures or tests to reliably allow differentiation between these subtypes of SSI (23). Furthermore, diagnostic criteria for superficial SSI such as tenderness, redness, localized swelling and local heat are subject to interobserver variability (24). Therefore, previous studies addressing the effect of anesthesia on SSI, yield less reliable results compared to this study using objectified PJI as the primary outcome measure.

The IDSA guidelines dictate a vigorous surgical treatment for (suspected) SSI following TJA including surgical debridement and rinsing of the implant (25). In previous studies these guidelines were not applied and as such the diagnosis of actual early PJI was not reliably established.

To our knowledge this is the first study using the IDSA guidelines where an association between the type of anesthesia and the incidence of objectified early PJI (using the major MSIS criteria through the availability of at least 6 periprosthetic tissue cultures in every case with suspected infection) is shown. Our results indicate an increased risk of early PJI following TJA under general anesthesia, illustrated by an odds ratio of 2 (95% CI: 1.0 – 3.7). Although no longer statistically significant, subgroup analysis for the type of arthroplasty (THA or TKA) demonstrated similar confidence intervals which indicate these results are robust and do not seem to depend on type of arthroplasty.

So far, the mechanism by which general anesthesia might increase, or spinal anesthesia might reduce the incidence of infection is not fully understood. However, increased tissue oxygenation (through reduced postoperative pain and the direct vasodilatory effect of spinal anesthesia) has been suggested as a potential mechanism in the past (26).

Next to these beneficial effects on tissue oxygenation, neuraxial anesthesia is also associated with reduced blood loss, a reduced requirement of blood transfusions and a reduced incidence of hyperglycemia. All these factors are known for their immunosuppressive effects (27, 28).

Besides the suggestion of protective effects of spinal anesthesia several aesthetic agents which are commonly used in general anesthesia, may significantly inhibit leukocyte chemotactic migration, phagocytosis, lymphocyte function, inflammation or even directly support bacterial growth in case of contamination (5). Furthermore, studies comparing general and spinal anesthesia showed that in spinal anesthesia these immunosuppressive effects were minimal (29).

On the other hand, one could speculate on a potential negative effect of spinal anesthesia on the incidence of early PJI induced by intra-operative hypothermia, which has been associated with an increased incidence of SSIs in other surgical specialties and is more prevalent during spinal anesthesia (30). However, despite the latter, spinal anesthesia was still associated with a reduced risk of early PJI in our study.

Limitations

First, due to the observational nature of the study, confounding (by indication) cannot be precluded. To control for this potential confounding, we matched patients based on propensity scores. Although matching of patients was successfully performed based on a subset of baseline characteristics, differences could theoretically still exist in unmeasured covariates (e.g. diabetes mellitus, rheumatoid arthritis and anticoagulant usage in this study) resulting in residual confounding. Anticoagulant therapy, for example, is generally considered as a contra-indication for the application of spinal anesthesia. This may have caused allocation of anticoagulant users to the general anesthesia group. However, since protocols for perioperative interruption of anticoagulant use (with or without bridging) are readily available and mandatory regarding elective TJA in our clinic, anticoagulant therapy is unlikely to cause allocation of patients towards the general anesthesia group. Furthermore, both diabetes and rheumatoid arthritis do not influence the choice for either spinal or general anesthesia in our hospital.

Another limitation is the fact that our data are sourced from 1 hospital only. Therefore, the major question remains whether our data and drawn conclusions will be reproducible in studies on, for example, national joint registries. However, on the other hand this last limitation warranted that a complete follow-up could be guaranteed and that no PJIs could have been missed.

In conclusion, this is the first study to suggest a potential association between general anesthesia and an increased risk of early PJI. This clinically relevant finding should encourage the set-up of future research using (multi-center) randomized large-scale data and national joint registry studies.

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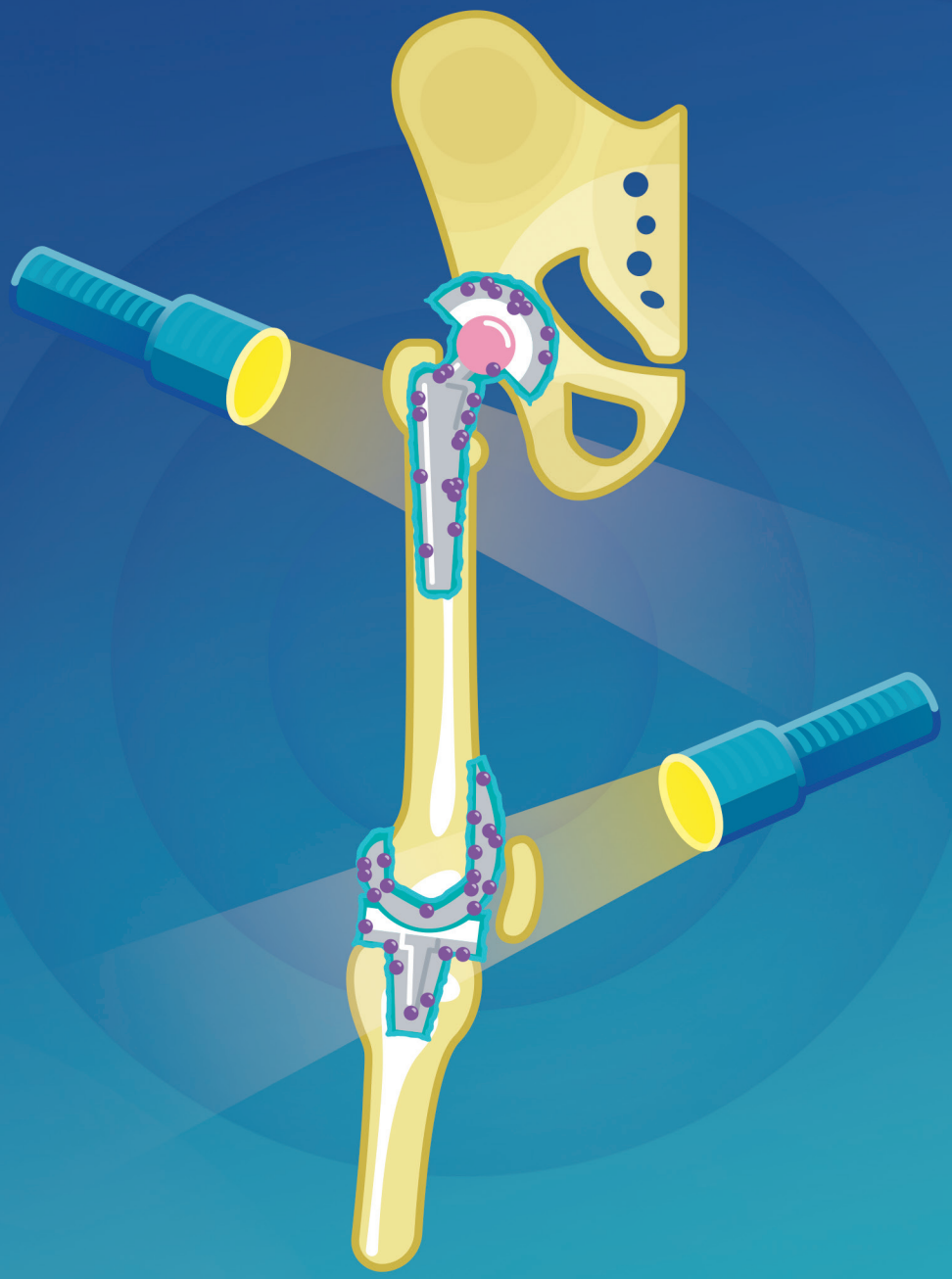

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Low sensitivity of the Synovasure® lateral flow test for intraoperative exclusion of prosthetic joint infection

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ABSTRACT

Introduction: The Synovasure lateral flow test (Synovasure®) was developed as a rapid test for the detection or exclusion of periprosthetic joint infection (PJI). 3 studies have reported promising results on its diagnostic value in total joint revision surgery. We aimed to assess the sensitivity and specificity of the Synovasure test to exclude infection in patients undergoing revision surgery for suspected early aseptic loosening of a total hip or knee arthroplasty.

Materials & Methods: In a prospective study design, 37 patients that underwent revision surgery for suspected early aseptic loosening (<3 years after primary arthroplasty) were included. The Synovasure® test was used intraoperatively to confirm the aseptic nature of the loosening and 6 tissue-cultures were obtained in all cases. Exclusion criteria were patients with a preoperatively confirmed PJI, acute revisions (<90 days after primary arthroplasty) and cases with malpositioning, wear or instability of the prosthesis.

Results: 5 of the 37 patients were diagnosed with a PJI based on the intra-operative tissue cultures. In only 1 out of these 5 cases this was confirmed by the intra-operative Synovasure test. No tests were falsely positive.

Conclusion: In this case series the Synovasure lateral flow test had a low sensitivity to exclude PJI in patients with suspected aseptic loosening. The role of the Synovasure lateral flow test in the intra-operative exclusion of PJI during revision surgery for suspected early aseptic loosening appears to be more limited than previously indicated.

INTRODUCTION

Periprosthetic joint infection (PJI) accounts for up to 25% of failed total knee arthroplasties (TKA) and up to 15% of failed total hip arthroplasties (THA) (1, 2).

Distinguishing the septic- from the aseptic failures in total joint arthroplasty (TJA) is critical in the successful treatment of the painful prosthetic joints, as they require different surgical strategies. To this end, the Musculoskeletal Infection Society has formulated criteria for decision-making in the work-up of suspected of PJI (3). However, this work-up remains far from straight forward, mainly since there is no uniform test for diagnosing PJI (3). Therefore, a simple diagnostic tool for PJI would be important.

Recently, the presence of the α-defensin biomarker in synovial fluid was suggested as a possible marker of periprosthetic joint infection, since it is naturally released by neutrophils in the presence of synovial fluid pathogens (4, 5). 3 studies using quantitative measurements of α-defensin have reported a sensitivity and specificity above 96% for PJI (6-8).

From these reported high sensitivity and specificity of α-defensin levels in detecting PJI, the Synovasure test (Zimmer Inc., Warsaw, Indiana), a lateral flow test for the detection of α-defensin levels, has been made commercially available. The Synovasure lateral flow (Synovasure®) test is a rapid measure of the α-defensin levels in synovial fluid, and provides dichotomic results after 10 minutes. 2 studies reported a sensitivity (67-69%) and specificity (93-94%) lower than in the previously mentioned quantitative measurements (9, 10). However, a recent study by Berger et al. reported higher sensitivity (97%) and specificity (97%) (11).

The previously mentioned studies were performed in non-specific patient populations containing varying indications for revision surgery ranging from evident acute PJI to reimplantation in 2-stage PJI revisions. However, the true clinical value of this promising test may lie in its ability to intraoperatively distinguish the early (<3 years following implantation) aseptic failure, where a 1 stage revision is indicated, from the early septic failure with less virulent micro-organisms where a staged revision would be more appropriate.

In this study we evaluated the additional value of the intraoperative Synovasure lateral flow test in confirming the absence of PJI in a group of patients undergoing prosthetic joint revision surgery for suspected early aseptic loosening. The results of the Synovasure test were compared with intraoperative tissue cultures.

Furthermore, we assessed the possible correlation of false-negative test results with the presence of metallosis, since previous studies have suggested that metallosis may predispose to false-positive results (12).

MATERIALS & METHODS

Since August 2015, the Synovasure® test is being used in our clinic as an adjunct tool to exclude PJI intraoperatively in revision patients with suspected early aseptic loosening of the implanted THA or TKA. Cases were prospectively included in the presence of a chronically painful (>90 days) prosthetic joint who underwent revision surgery due to suspected early aseptic loosening (<3 years after primary arthroplasty) of the implant after TKA or THA between August 2015 and October 2017. During revision surgery on these patients in this period, the Synovasure® test was used to aid in the exclusion of PJI. Excluded from this study were patients already diagnosed with PJI according to the MSIS criteria, acute revisions (<90 days), revisions due to dislocations, revisions due to malpositioning, or cases where an insufficient amount of synovial fluid could be aspirated to perform the Synovasure lateral flow test.

In all cases, synovial fluid was aspirated under aseptic conditions (after surgical dissection up to the joint capsule) from the affected joint whilst avoiding any contamination with blood. The Synovasure® test was carried out according to the manufacturer's instructions. In case of a positive Synovasure test, we considered the joint to be infected and proceeded with the removal of the prosthesis and implantation of a spacer containing antibiotics. If the test was negative, we proceeded with a one-stage revision of the affected joint. In all cases, a total of 6 microbiologic cultures of synovial tissue and the interface membrane were collected. The tissue samples were cultured for 14 days in the microbiology laboratory. Tissue cultures were considered positive for PJI when at least 2 out of 6 cultures grew identical pathogens. During surgery, the presence of metallosis or macroscopic signs of infection (presence of pus) were noted.

Ethics, funding and conflicts of interest

The procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation and with the Helsinki Declaration of 1975, as revised in 2000. This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors. No competing interests declared.

RESULTS

37 patients (22 men), mean age 66 (51-81) years, planned for revision surgery met the inclusion criteria. Revision surgery was performed on 8 hips and 29 knees. 5 patients were diagnosed with PJI due to positive tissue cultures. Out of these 1 patient had a positive Synovasure test and 4 patients tested negative. Thus, there were 1 true-positive Synovasure test, and 4 false-negative Synovasure tests (table 1). No false-positive Synovasure tests were observed, even in the presence of metallosis.

Table 1: Specification of the false-negative cases

False-negative case no.	Identified pathogens	Positive cultures
1	Staphylococcus Epidermidis	2/6
2	Staphylococcus Epidermidis	3/6
3	Staphylococcus Epidermidis & Staphylococcus Saccharolyticus	2/6
4	Propionibacterium Acnes	2/6

4 false-negative cases were observed, all these patients were treated as 1-stage revisions for PJI with adequate antibiotics over the course of 12 weeks.

The only true positive test occurred in a patient with intraoperative macroscopic signs of infection due to the presence of pus. In this patient, previous tests did not indicate PJI according to the MSIS criteria, however, 6 intraoperative tissue cultures grew Staphylococcus Epidermidis. 29 true negative tests were observed, in one of these cases metallosis was present during surgery. Table II contains the statistical details on the diagnostic characteristics of the Synovasure® test in our study population.

DISCUSSION

The identified sensitivity (1/5) is clearly lower than reported in previous studies (9-11). These 3 earlier studies reported a sensitivity of 67-97% and specificity of 93-96% of the Synovasure® test for the diagnosis of PJI

In contrast to our study these studies included various kinds of procedures, namely: patients fulfilling the MSIS criteria for PJI preoperatively, 1-stage revisions, re-implantations at second-stage revision, explantations and spacer-implantations, spacer exchanges, debridement's with exchange of mobile parts and retention of the prosthesis and excision of a hip prosthesis (10). Kasparek et al. (2016) also included cases with varying indications: aseptic loosening, polyethylene wear with osteolysis, suspected chronic PJI, patients fulfilling the MSIS criteria for PJI preoperatively, instability and stiffness. Berger et al. (2017) included patients fulfilling a modified version of the MSIS criteria for PJI preoperatively. This modification, and the non-specific patient populations including varying indications for revision surgery, makes the reported values difficult to interpret and compare. Even more so in establishing the tests' ability to distinguish the early aseptic failure from the septic failure in unclear cases which are not evidently infected (not fulfilling the modified MSIS criteria for PJI).

In contrast to these earlier studies our study population focused on the ability of the Synovasure test to exclude PJI in a uniform subgroup of patients undergoing revision surgery for suspected early aseptic loosening. To our knowledge, this is the first study to assess the Synovasure® lateral flow test in this specific homogenous subgroup of patients. From clinical practice this is an important strength of our study and as such is the finding of a rather low sensitivity in this particular subgroup. This strength has to be balanced against the limitation of a rather small number of patients included which warrant caution in drawing firm conclusions. Another strength of our study, and the one from Sigmund et al. (2017), is that there is no conflict of interest in relation to the manufacturer of the Synovasure test (10).

Previous studies have suggested that the presence of metallosis may predispose to false-positive results of the Synovasure test. In our study, there was 1 case of metallosis, which yielded a negative Synovasure test.

Our findings indicate that the Synovasure lateral flow test has limited additional value for the intraoperative exclusion of PJI from low virulent micro-organisms (i.e. Staphylococcus Epidermidis and Proprioni Acnes) in a homogenous subgroup of patients with suspected early aseptic failures of THA and TKA.

This is an important limitation in the clinical use of the test, which initially promised to be ideal in simply confirming or excluding any PJI intra-operatively. The sensitivity may be improved by aiming future research on fine-tuning the thresholds of α-defensin in the presence of low-virulent micro-organisms. This may however be difficult to achieve since recent reviews failed to establish a more accurate cut-off value. The latter was due to the usage of different techniques among laboratories and a shortage of well-designed studies (13, 14).

It should also be noted that the dichotomic nature of the Synovasure® lateral flow test, where the presence or absence of a PJI is claimed, is another limitation. Irrespective the fact that a solution may be found to decrease the relatively high chance of a false negative test outcome in case of low virulent agents, still the microbial agents and their resistance patterns would have to be obtained from prolonged tissue cultures.

For that reason future research should also continue to focus on advances in molecular microbiology and techniques for detecting microbial infections(e.g. susceptibility testing, DNA amplification assays) (15). These techniques may offer increased diagnostic resolution and are not dichotomic by also providing information on the causative pathogen's identity and resistance pattern. Further improvement on these earlier mentioned microbial detection techniques may eventually bypass the dependency on tissue cultures for adequate antibiotic treatment.

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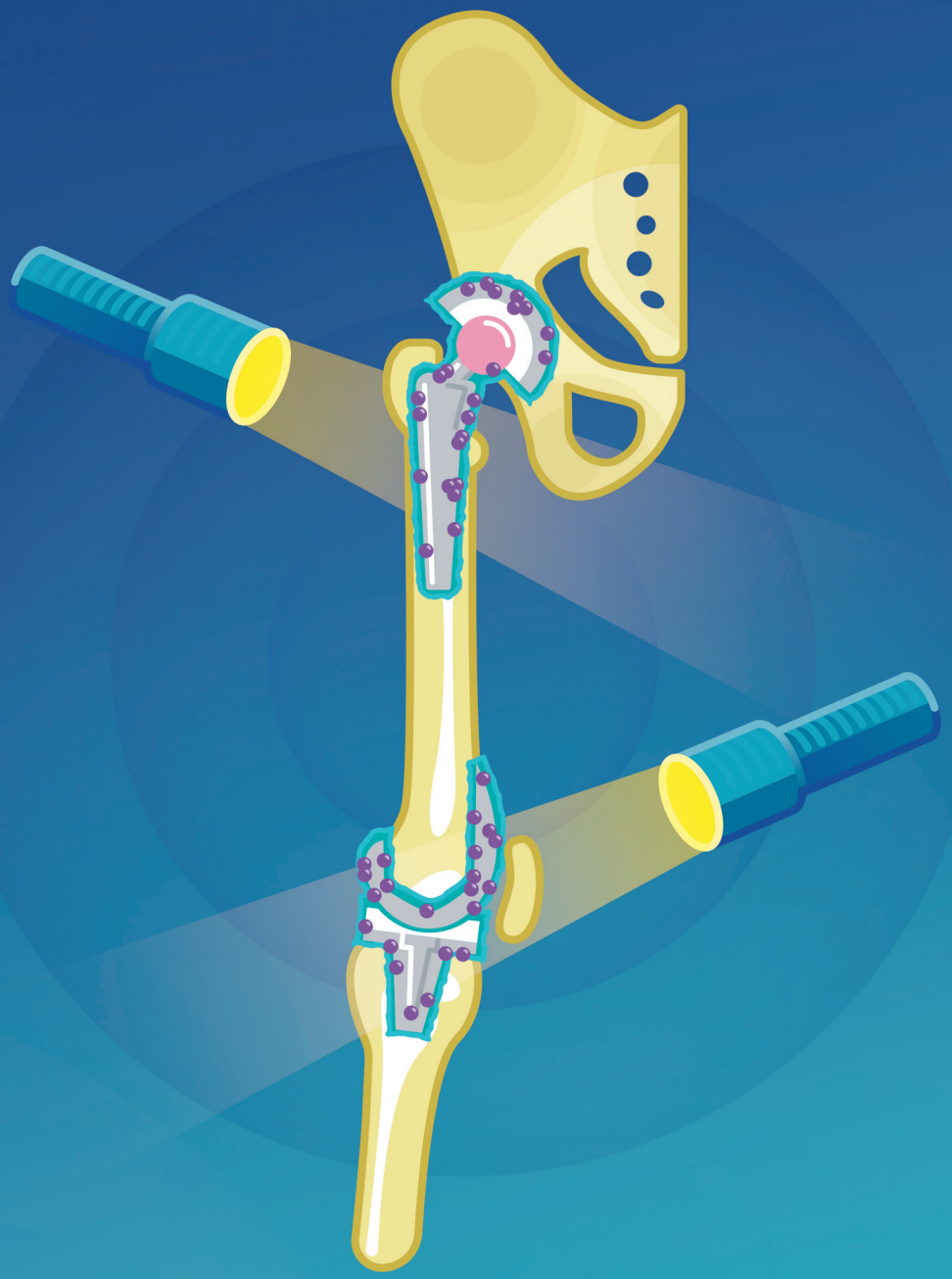

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Empiric antibiotic therapy in early periprosthetic joint infection: a retrospective cohort study

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ABSTRACT

Introduction: Periprosthetic joint infection (PJI) is a devastating complication following total knee or total hip arthroplasty (TKA/THA). Appropriate empiric antibiotic treatment, initiated directly after debridement and implant retention (DAIR), is suggested to contribute to treatment success. The aim of this study was to describe the microbiology and the antibiotic susceptibility in early PJI to guide future empiric treatment in a region with a low incidence of methicillin resistant *Staphylococcus aureus* (MRSA).

Materials & Methods: Consecutive patients who underwent DAIR within 3 months after primary unilateral TKA or THA between January 2011 and December 2018 were retrospectively identified from the hospital electronic health records. Data on causative pathogens, antimicrobial susceptibility and the number of post-operative days until cultures demonstrated bacterial growth were collected.

Results: 111 early PJIs were identified of which 65 (59%) were monomicrobial and 46 (41%) polymicrobial. Among all isolated pathogens, *Staphylococcus aureus* (n=53; 29%) was the most commonly identified pathogen in early PJI without any involvement of MRSA. 72% of PJIs were susceptible to vancomycin which could be increased to around 90% by adding gram-negative coverage. On the 5th postoperative days, bacterial growth was observed in 98% of cases. All gram-negative bacteria demonstrated positive tissue cultures on the 4th postoperative day.

Conclusion: Vancomycin combined with ciprofloxacin or a third generation cephalosporin had the highest antimicrobial coverage of the pathogens identified in early PJI. Empiric treatment of gram-negative treatment can be safely terminated in the absence of gram-negative pathogens after 4 days of culturing in cases without preoperative antibiotic treatment.

INTRODUCTION

Periprosthetic joint infection (PJI) is one of the most serious complications following total knee or hip arthroplasty (TKA/THA) and accounts for up to 25% of failed TKA and 15% of failed THA (1, 2). The annual number of THAs and TKAs are projected to increase substantially (3) which will eventually also lead to an increase in PJI cases.

PJI can be subdivided into early (<3 months after surgery), delayed (3-12 months after surgery) and late (>1 year after surgery) infections (4). Early PJI is the most frequently encountered subtype and is generally treated by means of debridement, antibiotics and implant retention (DAIR) with varying success rates (23 – 100%) (5, 6).

Several studies have suggested factors associated with an improved treatment outcome of DAIR. These factors include, absence of renal- and/or liver failure, uncemented arthroplasty, failure timely initiation of DAIR (< 3 weeks of onset of symptoms), absence of MRSA amongst the pathogens, and exchange of mobile parts (7-9). Despite ongoing efforts to elucidate the effectiveness of DAIR, empiric antibiotic treatment remains an understudied aspect even though several scientific associations between ineffective empiric therapy and treatment failure have been suggested (10, 11).

Following DAIR, empiric antibiotic therapy should be commenced directly after surgery. Since the results of the intra-operative tissue cultures are only available a few days after surgery, the post-surgery choice of antibiotics is usually aimed at the organisms most likely to cause the PJI (12). Because biofilm formation in PJI starts directly after exposure to the pathogen (13), rapid exposure of the causative pathogen to an adequate antibiotic agent is believed to contribute to treatment success (10, 11).

In the past few years concerns have been raised about the increase of antibiotic resistance among pathogens causing PJI. For example, research has suggested that methicillin resistance among coagulase negative staphylococci (CNS) strains in PJI has increased from 2% (14) to 75% in more recent years (15, 16). Current (American) guidelines advocate the empiric use of a broad spectrum β-lactam combined with vancomycin (6) and in the past, a British study recommended the use of vancomycin combined with a carbapenem (17). Unfortunately, the spectrum of causative pathogens differs between countries and regions (18). Considering the latter, these previous recommendations may not be applicable to regions associated with a low incidence of methicillin resistant *Staphylococcus aureus* (MRSA) where vancomycin is used as a second resort in case of proven resistance to, or contraindications for other (less toxic or more effective) antibiotics. Therefore, the aim of this study was

to describe the spectrum of causative pathogens and the corresponding antibiotic resistance patterns in a large general teaching hospital in the Netherlands. Using this information, we aim to provide guidance on the optimization of the empiric treatment of early PJI in this region associated with a low incidence of MRSA.

MATERIALS & METHODS

All consecutive patients who underwent debridement (with or without concomitant exchange of mobile parts), antibiotics and implant retention (DAIR) surgery within 3 months after primary unilateral TKA or THA between January 2011 and December 2018 were retrospectively identified from hospital electronic health records of a large Dutch teaching hospital.

Cases with eventual negative tissue cultures or patients that had received preoperative antibiotic treatment were excluded. Cases were also excluded if patients underwent early revision surgery preceding DAIR for aseptic failure or in the presence of positive tissue cultures obtained during primary implantation.

Patient records were reviewed to retrieve gender, age, the American Society of Anesthesiologist's (ASA) classification at the time of THA or TKA implantation, cement use during index implantation as well as up to 6 tissue culture results along with the corresponding antibiotic resistance patterns obtained during DAIR. Furthermore, the number of postoperative days until tissue cultures demonstrated bacterial growth and the time until the determination of the corresponding antibiotic susceptibilities was retrieved. Antibiotic susceptibility was compared for 9 potential empiric treatment strategies: flucloxacillin, amoxicillin-clavulanic acid, cefazolin, cefuroxime, ciprofloxacin, ceftriaxone, or vancomycin monotherapy, and for vancomycin plus either ceftriaxone or ciprofloxacin combination therapy.

Data related to any subsequent DAIR procedures were excluded. PJI was diagnosed according to the major Musculoskeletal Infection Society (MSIS) criteria by means of 2 or more tissue cultures demonstrating growth of an identical pathogen (19).

Furthermore, the Dutch national joint registry was consulted to verify that no cases were missed that underwent revision surgery elsewhere.

The study received approval of the Rijnstate Committee for Research Involving Human Subjects that granted a waiver of informed consent (study number: 2018-1333). Statistical analysis was performed using SAS 9.4 (SAS Institute Inc).

Surgery Protocol

All patients were screened for nasal carriage of *S. aureus* through nasal swab cultures. Confirmed carriers were instructed to apply mupirocin ointment (20 mg/g) in the nares three times a day and to use chlorhexidine soap (40 mg/ml) once daily to wash their body and hair. This eradication treatment was started three days before surgery and continued for five days.

Within an hour before the index arthroplasty surgery patients received prophylactic administration of cefazolin. Antibiotic prophylaxis was discontinued 24 hours postoperatively. All patients underwent THA by posterolateral approach. Poor bone quality, bone loss or age >75 years were indications for cemented (Exeter®; Stryker Howmedica) THA. Otherwise uncemented implants (Zweymuller®; Zimmer up to 2014 and from then on CLS Spotorno®/Allofit; Zimmer) were used. All TKAs were performed using cemented implants (LCS®, DePuy Synthes) through a medial parapatellar arthrotomy. Bone cement (Palacos G®; Heraeus) in both TKA and THA contained gentamicin. All patients were subjected to prospective surveillance of PJI for at least 3 months after surgery. In case of a suspected early infection (persistent wound leakage 10 days after primary THA/TKA, fever, rising levels of C-reactive protein) DAIR with exchange of mobile parts was performed and six intra-articular tissue cultures were obtained. Awaiting culture results, empiric treatment with intravenous antibiotics (flucloxacillin 8 grams every 24 hours through continuous infusion) was initiated according to the hospital protocol.

Microbiological methods

The obtained tissue biopsies were homogenized and inoculated onto sheep blood, chocolate, MacConkey, fastidious anaerobe, and neomycin anaerobic blood agars (Oxoid Ltd., Basingstoke, UK) and incubated at 35°C for 10 days. Sheep blood and chocolate agars were incubated at 5% CO2; MacConkey at 5% O2; and the anaerobic agars were incubated anaerobically. In addition, 0.2 mL of the homogenized substance was inoculated into brain heart infusion broth (Brewer, Oxoid Ltd., Basingstoke, UK) and incubated at 35°C. At day 4 of the 7-day (until mid-2016) or day 6 of the 10-day incubation period, or earlier if cloudy, 0.1 mL of broth was subcultured on chocolate agar, fastidious anaerobe, and neomycin anaerobic blood agars for 3 (until 2016) or 4 days. Microorganisms were identified with the use of a Bruker Biotyper MALDI-TOF MS (Bruker, Bremen, Germany). Antibiotic resistance patterns were registered per patient.

Statistical methods

The coverage of nine potential empiric treatment strategies (flucloxacillin, amoxicillin-clavulanic acid, cefazolin, cefuroxime, ceftriaxone, or vancomycin monotherapy, and

vancomycin plus ceftriaxone or ciprofloxacin combination therapy) was studied. In the presence of polymicrobial infections a cumulative sensitivity pattern was formulated (eg. if one or more pathogens of a polymicrobial infection were resistant to an antibiotic, the case would be registered as resistant to this antibiotic regimen). Percentages were compared to reveal the antibiotic regiment that yielded the highest sensitivity rate.

RESULTS

A total of 160 cases were identified from the electronic health records. Forty-nine (31%) patients were excluded since tissue cultures remained negative, leaving 111 cases for analysis. Patient demographics are presented in table 1. Through consultation of the Dutch national joint registry, no cases were identified that underwent early revision surgery elsewhere related to infection.

Among these 111 cases, 65 (59%) were monomicrobial and 46 (41%) were polymicrobial infections. Eighty-one (73%) cases were infected with gram-positive pathogens only and 11 (10%) cases with gram-negative pathogens (table 2). All isolated pathogens and their frequency of involvement are displayed in table 3. *Staphylococcus aureus* was the most commonly identified species (29%, table 2). The cumulative susceptibilities of nine potential empiric antibiotic regimens are displayed in figure 1, identifying vancomycin as the superior antibiotic agent regarding *in vitro* antibiotic coverage. Combination therapy of vancomycin and ciprofloxacin or a third-generation cephalosporin yielded the highest coverage (88-92%).

The mean number of days until bacterial growth was 2.5 ± 1.2 days (range: 1 – 9 days). In 108 (98%) cases, the first positive tissue culture results were obtained within five postoperative days (figure 2). Two cultures (1.8%) showed growth later, respectively after 6 days (*Corynebacterium* species) and 9 days (*Cutibacterium acnes*). In a single case, data on the time to culture results were missing. Gram-negative pathogens grew after a maximum of 4 days whereas gram positive pathogens took up to 10 days to grow (figure 3). Antibiotic susceptibilities were available after a mean of 3.7 ± 1.6 days (range: 2 – 13 days).

Table 1: Patient demographics.

Characteristic		Value
Age (mean, SD, Range)		69.2, 10.7, 23 – 89.
Gender		
	Male (n (%))	58 (52.3%)
	Female (n (%))	53 (47.7%)
Joint		
	Knee (n (%))	31 (27.9%)
	Hip (n (%))	80 (72.1%)
Indication for arthroplasty		
	Osteoarthritis (n (%))	101 (91%)
	Fracture (n (%))	2 (1.8%)
	Malunion (n (%))	3 (2.7%)
	Osteonecrosis (n (%))	3 (2.7%)
	Non-union (n (%))	2 (1.8%)
Cement usage		
	Cementless (n (%))	40 (36%)
	Cemented (n (%))	71 (64%)
ASA-classification		
	1 (n (%))	16 (14.4%)
	2 (n (%))	57 (51.4%)
	3 (n (%))	30 (27%)
	4 (n (%))	3 (2.7%)
	Missing (n (%))	5 (4.5%)

SD: Standard Deviation, ASA: American Society of Anesthesiologists.

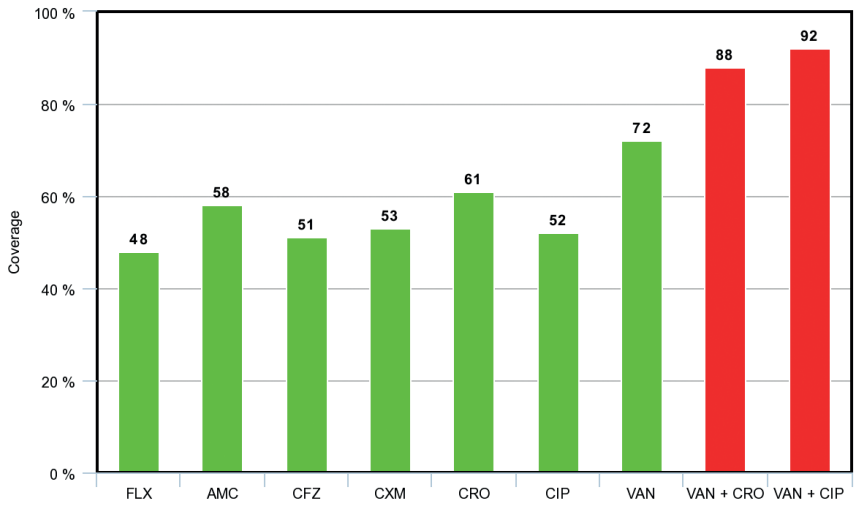

Figure 1: Bar chart illustrating the percentage of cases susceptible to the different empiric antibiotic regimens.

Green bars represent monotherapy, red bars represent combination therapy. FLX: flucloxacillin, AMC: amoxicillin-clavulanic acid, CFZ: cefazolin, CXM: cefuroxime, CRO: ceftriaxone, CIP: ciprofloxacin, VAN: vancomycin.

Table 2: Overview of the characteristics of each PJI in the left column. In the right column the identified pathogens and the number of cases in which they were involved, sorted according to their relevant subgroups.

Type of infection	n	%	Pathogen subgroup	n	%
			Staphylococcus aureus	53	29%
Monomicrobial	65	59%	Coagulase negative *Staphylococcus*	37	20%
Polymicrobial	46	41%	Enterobacterales	31	17%
			Streptococcus species	19	11%
Gram-positive only	81	73%	*Enterococcus species*	15	8%
Gram-negative only	11	10%	*Corynebacterium species*	10	6%
Mixed gram-positive & gram-negative	19	17%	*Pseudomonas aeruginosa*	6	3%
			Other	11	6%

Table 3: overview of the numbers and percentages of all individually isolated pathogen species.

Pathogen species	n	%
Staphylococcus aureus	53	29.1%
Coagulase Negative Staphylococcus	37	20.0%
Enterococcus faecalis	14	7.7%
Corynebacterium species	11	5.9%
Proteus mirabilis	9	4.9%
Streptococcus agalactiae	8	4.4%
Escherichia coli	7	3.8%
Pseudomonas aeruginosa	6	3.3%
Enterobacter cloacae	5	2.7%
Group G streptococcus	4	2.2%
Morganella morganii	3	1.6%
Cutibacterium acnes	3	1.6%
Serratia marcescens	3	1.6%
Group C streptococcus	2	1.1%
Klebsiella oxytoca	2	1.1%
Streptococcus oralis	2	1.1%
Eikenella corrodens	1	0.5%
Enterococcus faecium	1	0.5%
Finegoldia magna	1	0.5%
Granulicatella adiacens	1	0.5%
Klebsiella pneumoniae	1	0.5%
Kocuria species	1	0.5%
Micrococcus luteus	1	0.5%
Peptoniphilus harei	1	0.5%
Peptopstreptococcus species	1	0.5%
Proteus vulgaris	1	0.5%
Stenotrophomonas maltophilia	1	0.5%
Streptococcus pyogenes	1	0.5%
Streptococcus sanguinis	1	0.5%

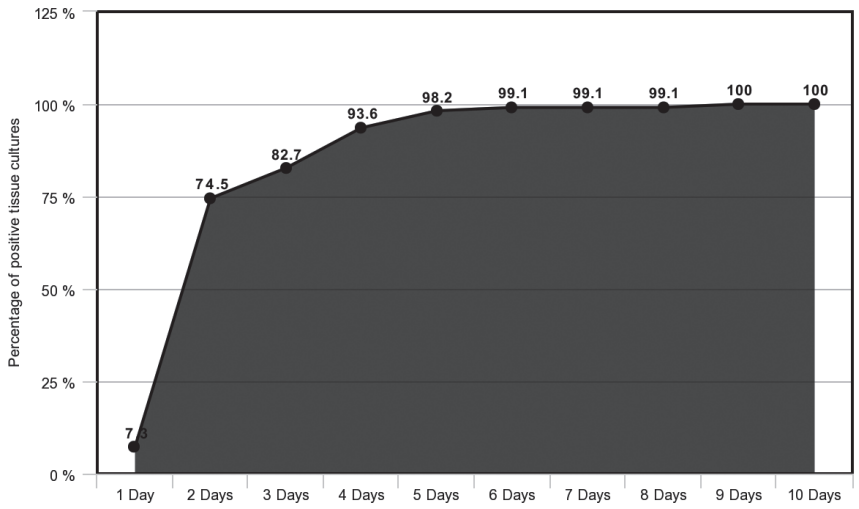

Figure 2: Area chart illustrating the percentage of cases (n = 110) with postoperative positive tissue cultures on the Y-axis and the number of postoperative days on the Y-axis.

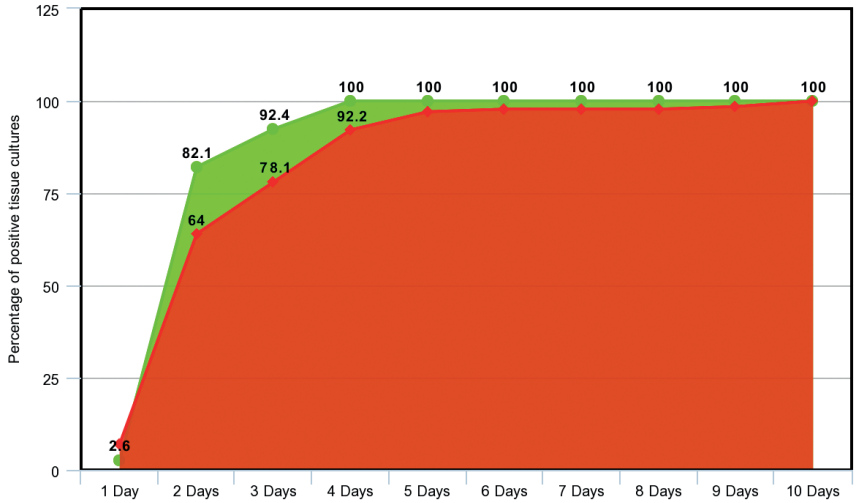

Figure 3: Area chart illustrating the percentage of either gram negative (n = 39, displayed in green) or gram positive pathogens (n = 142, displayed in red) and the number of postoperative days until positive tissue cultures appeared.

DISCUSSION

Staphylococcus aureus was the most commonly identified pathogen in early PJI in this study, notably without any involvement of MRSA. Despite the absence of MRSA, cumulative antimicrobial susceptibility demonstrated vancomycin as the empiric agent that yielded the highest coverage due. Furthermore, 41% of PJIs were polymicrobial in nature which underlines the importance of broad-spectrum empiric antibiotic treatment.

The identification of *Staphylococcus aureus* and CNS as the most prevalent pathogens and the spectrum of other isolated pathogens in this study is in line with the results of several previous studies from different topographic regions describing the microbiology of PJI (16, 17, 20-23). However, this is the first study to specifically address causative pathogens in early PJI and the corresponding spectrum of antimicrobial susceptibility. Only a few previous studies have provided specific recommendations on the optimal empiric antibiotic treatment whilst taking this antimicrobial susceptibility into account. For example, Moran et. al recommended the use of vancomycin combined with a carbapenem whereas Fulkerson et al. had previously recommended the specific use of either vancomycin or a 3rd or 4th generation cephalosporin (16, 17). Two more recent studies also recommended vancomycin as the designated empiric agent, however the common denominator regarding these studies is a relatively high incidence of MRSA (24, 25). The generalizability of these recommendations to regions with low incidences of MRSA is therefore questionable (26). Recently, a Dutch study recommended the use of cefazolin for the empiric treatment of PJI (21). However, only 3 different potential empiric antibiotic agents were incorporated in their analysis and vancomycin was not investigated. Taken together, there is no consensus on the optimal choice of empiric antibiotic treatment. From the studies presented there appears to be a tendency towards advocating vancomycin as the empiric treatment of choice in particular for regions with MRSA. In our study, no infections with MRSA occurred and still vancomycin had the highest coverage of all monotherapeutic antibiotic regimens that were analyzed. The coverage could be further increased by adding ceftriaxone or ciprofloxacin to cover gram-negative pathogens.

However, one should consider vancomycin's important disadvantages such as increased toxicity compared to beta-lactam antibiotics, necessity for blood level measurements, its decreased effectiveness against methicillin sensitive *Staphylococcus aureus*, and its suboptimal activity in biofilms (27-29).

It is important to note that a high coverage does not necessarily imply high efficacy. Reaction with the components of the biofilm matrix reduces the ability of several antibiotics to penetrate the biofilm which results in a reduced exposure of bacteria to the antibiotics and a subsequent decrease in antibiotic action (30).

Timely termination of empiric antibiotics when cultures remain negative could reduce the costs associated with unnecessary administration of antibiotics, reduce the in-hospital stay, decrease the emergence of resistant organisms, and reduce the risk of potential side effects related to antibiotic toxicity. The proposition to reduce the duration of the post-operative antibiotic therapy is not new and it has recently been proposed to reduce the coverage of gram-negative bacilli to not more than 3 days (31). These results match our findings with gram negative pathogens growing before day 4 (figure 3). These combined findings suggest that empiric treatment of gram negative pathogens can be safely terminated on day 4 in case of no growth of gram negative pathogens by that timepoint.

Among all included cases, 98% of all cultures demonstrated bacterial (gram-positive or gram-negative) growth by the fifth day. Based on this result and considering that 30% of primary DAIR procedures were excluded because PJI was ruled out, termination of empiric antibiotics in certain cases might be considered in cases with a low suspicion of infection. Obviously, the decision to terminate antibiotics in patients with preoperatively administered antibiotics should be considered with care.

Limitations

The major limitation of this study is its retrospective design. Furthermore, the present study is a single-center study and therefore may yield institute-specific results since the spectrum of isolated pathogens in early PJI may be dependent of pre- and peri-operative anti-septic measures including the designated prophylactic antibiotics. Also, antibiotic-loaded cemented or cementless THA may influence the spectrum of isolated pathogens.

Conclusion

Effective empiric treatment has been associated with improved treatment outcomes in the treatment of PJI. A combination of vancomycin and ciprofloxacin or a third-generation cephalosporin had the highest antibiotic coverage in early PJI, even in the setting of a low incidence of MRSA. The American recommendation of vancomycin as part of an empiric treatment regime for early PJI therefore also seems applicable for regions with a low incidence of MRSA. However, this knowledge has to be balanced against other factors such as potential side effects and biofilm penetration. Empiric treatment of gram-negative pathogens can be safely terminated in the absence of gram negative pathogens in the tissue cultures on the 4th postoperative day. In addition, if cultures remain sterile up to day 5 early PJI becomes highly unlikely and complete termination of empiric treatment could be considered. However, great care should be undertaken in the decision to terminate treatment in patients that received preoperative antibiotics.

Conflict of Interest

All authors certify that they have no affiliations with or involvement in any organization or entity with any financial interest (such as honoraria; educational grants; participation in speakers' bureaus; membership, employment, consultancies, stock ownership, or other equity interest; and expert testimony or patent-licensing arrangements), or non-financial interest (such as personal or professional relationships, affiliations, knowledge or beliefs) in the subject matter or materials discussed in this manuscript.

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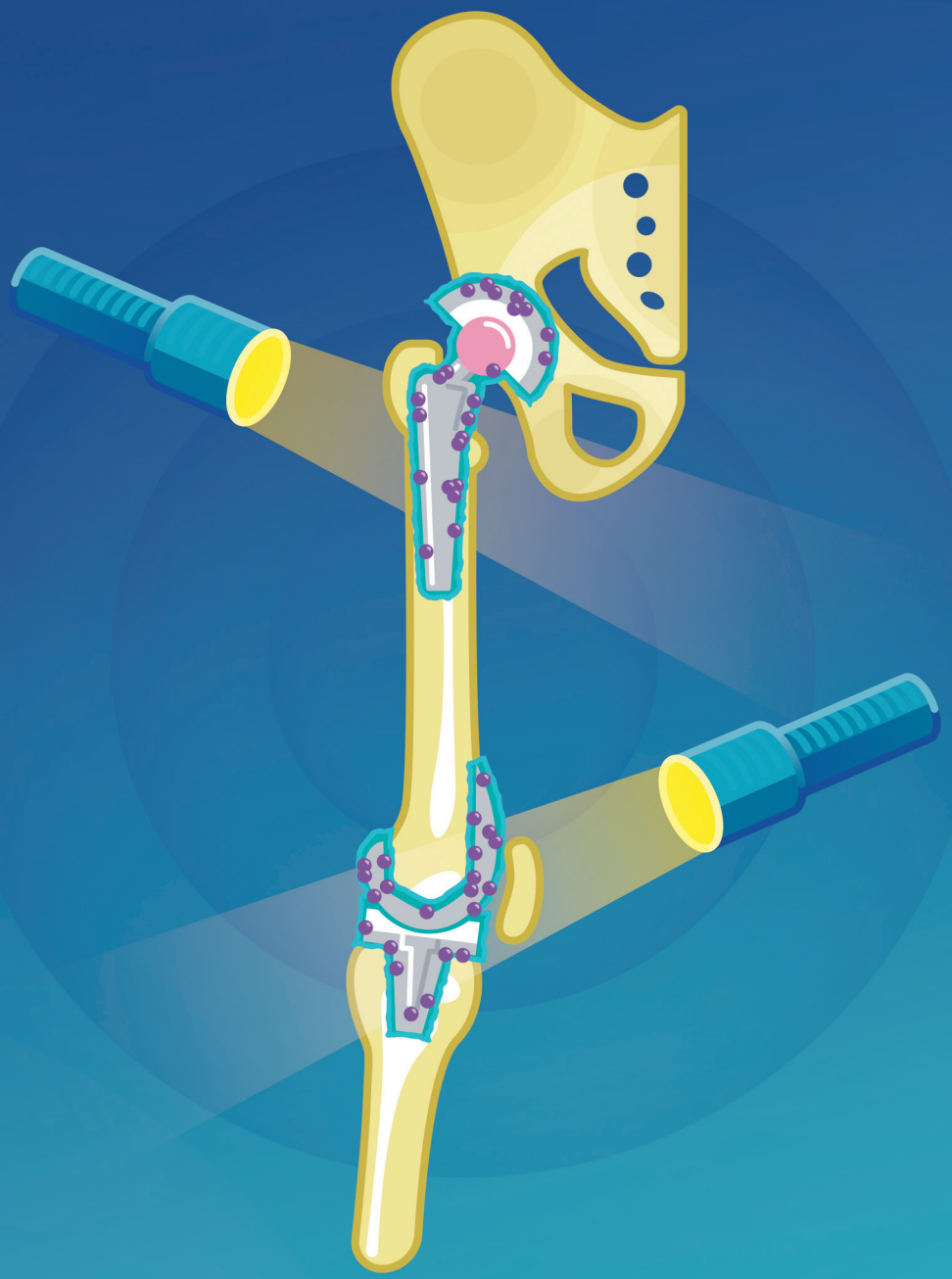

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The value of repeated debridement, antibiotics, and implant retention (DAIR) for early periprosthetic joint infection

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ABSTRACT

Introduction: Debridement, Antibiotics and Implant Retention (DAIR) is the proposed initial treatment of early periprosthetic joint infection (PJI) but may fail to provide infection control. Subsequently, either implant removal or repeated DAIR may be considered. This study aims to identify the failure rate of repeated DAIR for early PJI in primary total knee- and total hip arthroplasty (TKA/THA).

Materials & Methods: All DAIRs performed following primary THA or TKA for early PJI from 2010 to 2019 were retrospectively analysed. Patient demographics, comorbidities, surgical details, and pre-DAIR CRP levels were recorded. Failure of early infection control (within 1 month after DAIR) prompted a second DAIR. Follow-up was performed up to two years post-surgery. Kaplan-Meier survival analysis was performed in single and repeated DAIR groups. Cox regression analyses explored potential risk factors for implant failure after repeated DAIR.

Results: 124 cases of early PJIs were included. Single DAIR achieved adequate infection control in 69.4% (n = 86) of cases, while 30.6% (n = 38) underwent repeated DAIR within 3 – 23 days. After two years, implant removal was performed in 8 cases (9.9%; 95%CI 3.0% – 16.0%) in the single DAIR group and in 8 cases (22.2%; 95%CI 7.3% – 34.7%) in the repeated DAIR group. No statistically significant associations between failure of repeated DAIR and its potential risk factors were found.

Conclusion: If initial DAIR does not achieve early PJI control, repeated DAIR can still be considered since it may avoid implant removal in 77.8% of cases. Authors advocate tailored decisions considering implant revisability, patient comorbidity, and pathogen susceptibility.

INTRODUCTION

Periprosthetic joint infection (PJI) is a severe complication following total joint arthroplasty (TJA). For early PJI (occurring within 3 months of implantation), the standard treatment is Debridement, Antibiotics, and Implant Retention (DAIR) (1). Successful DAIR is defined by implant retention without infection signs after 12 weeks of antibiotics, with success rates reported between 26% and 92%. (2-10).

DAIR failures can be categorized as early failures (where infection control is not achieved) or late failures (where infection relapses after initial success) (11). Late failures typically involve implant loosening or bone loss, with associated symptoms like joint pain and elevated inflammatory markers. Early failures manifest through signs of progressive infection (i.e. wound breakdown, wound erythema, local pain and/or swelling, rising levels of C-reactive protein (CRP), fever or even sepsis). This study addresses treatment options if early DAIR fails to achieve infection control. In this case, the surgeons must decide whether to repeat DAIR or proceed with implant removal and revision surgery. While a repeated DAIR may seem appealing (since it omits the need for extensive revision surgery), its success rates are debatable (12). Most studies report on the outcome of single DAIR procedures and data on repeated DAIR procedures are limited in size and clarity, while commonly mixing early and late PJI cases (2, 8, 13-20). Based on the limited evidence on repeated DAIR procedures, the International Consensus on Orthopaedic Infections recommends considering revision arthroplasty following failed DAIR since additional DAIR procedures are, at best, equally effective as primary DAIR (12). However, if successful, repeated DAIR could be worthwhile due to its lower burden on patient and healthcare systems. The latter is supported by a study performed in 2020 that demonstrated that a second DAIR had a low failure rate and that therefore, a second DAIR should not be discarded in acute PJIs (21). Furthermore, a recent study retrospective multi-centre study demonstrated that a second DAIR can achieve a 83% success rate in selected patients (22).

To further elucidate on this common clinical dilemma, this study aimed to (1) identify the failure rate of a repeated DAIR procedure for unsuccessful early infection control in early PJI and (2) compare these results to the failure rate of a single DAIR with adequate early infection control. Furthermore (3), an exploratory analysis on potential procedure or patient related factors associated with treatment failure in cases that underwent repeated DAIR procedures was performed.

MATERIALS & METHODS

All patients who underwent a DAIR procedure between January 2010 and January 2019 within 3 months after primary elective unilateral total hip or knee arthroplasty (THA/TKA) were retrospectively identified from electronic health records at a large teaching hospital, excluding culture-negative cases.

Data collected included patient age, gender, American Society of Anaesthesiologists (ASA) classification, comorbidities (diabetes mellitus, chronic renal failure, liver failure, heart failure, coronary artery disease, stroke history, chronic obstructive pulmonary disease), body mass index (BMI), smoking status, joint age at the first DAIR, cement usage during the index procedure, tissue culture results after repeated DAIR and pre-DAIR CRP levels (first and any repeated DAIR). Additionally, the identity of causative pathogens was recorded. Demographic data of the patient cohort is displayed in Table 1.

Surgery Protocol

For primary THA or TKA, patients received 2 grams of cefazolin prophylactically 15 to 60 minutes before skin incision (THA) or tourniquet inflation (TKA), followed by three doses of 1 gram post-surgery at 8-hour intervals (23). THA was performed by, or under direct supervision of, senior hip surgeons. Accordingly, TKA was performed by, or under direct supervision of, senior knee surgeons. All TKA patients underwent surgery while using a tourniquet which was deflated after applying a pressure bandage over the affected knee. All TKAs were cemented and performed using a medial parapatellar arthrotomy. Both cemented and uncemented THAs were conducted using a posterolateral approach. The bone cement (Palacos® R+G; Heraeus) used in both TKA and THA contained 0.75 grams of gentamicin per 61.2 grams of powder.

Patients were closely monitored for post-operative infection signs and typically discharged only with a dry wound. Following discharge, all patients were subjected to protocolized surveillance of infection in the outpatient clinic for at least 3 months. In cases of wound drainage or prolonged drainage (>10 days post-surgery), blood samples were tested for CRP, erythrocyte sedimentation rate (ESR), and leukocyte counts. For suspected superficial surgical site infections (SSI) or wound breakdown, DAIR was performed.

Table 1: Demographic data of the patient cohort per group.

	Single DAIR group	Repeated DAIR group	SMD
N (number of patients)	86	38	
Age (median (IQR))	69 (64 - 77)	68 (61.5 - 77.5)	0.121
Male (%)	51 (59.3)	16 (42.1)	0.349
TKA (%)	25 (29.1)	11 (28.9)	0.003
Cemented prosthesis	50 (58.1)	25 (65.8)	0.158
Diabetes (%)	11 (12.8)	5 (13.2)	0.011
Active smoker (%)	13 (16.2)	12 (31.6)	0.365
History of Stroke (%)	7 (8.1)	4 (10.5)	0.082
Heartfailure (%)	9 (10.5)	2 (5.3)	0.194
Coronary disease (%)	13 (15.1)	5 (13.2)	0.056
BMI (median (IQR))	28.09 (24.46 - 32.76)	28.86 (25.97 - 34.21)	0.222
ASA (%)			0.444
	16 (18.8)	4 (10.5)	
	53 (62.4)	20 (52.6)	
	14 (16.5)	13 (34.2)	
	2 (2.4)	1 (2.6)	
Renal failure (%)			0.298
	44 (51.2)	17 (44.7)	
	34 (39.5)	16 (42.1)	
	6 (7.0)	3 (7.9)	
	1 (1.2)	2 (5.3)	
	0 (0.0)	0 (0.0)	
	1 (1.2)	0 (0.0)	
COPD (%)			
	81 (94.2)	32 (84.2)	0.363
	2 (2.3)	4 (10.5)	
	2 (2.3)	1 (2.6)	
	1 (1.2)	1 (2.6)	
	0 (0.0)	0 (0.0)	

SDM: Standardized Mean Difference, SD: Standard Deviation, TKA: Total Knee Arthroplasty, ASA: American Society of Anesthesiologists, Renal failure classified according to the five-stage kidney disease (G1: Kidney damage with normal or increased GFR (>90 mL/min/1.73 m2), G2: Mild reduction in GFR (60-89 mL/min/1.73 m2). G3a: Moderate reduction in GFR (45-59 mL/min/1.73 m2), G3b: Moderate reduction in GFR (30-44 mL/min/1.73 m2), G4: Severe reduction in GFR (15-29 mL/min/1.73 m2), G5: Kidney failure (GFR < 15 mL/min/1.73 m2 or dialysis). COPD: Chronic Obstructive Pulmonary Disease classified according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) criteria: GOLD Stage I: FEV1 ≥80% predicted, GOLD Stage II: FEV1 ≥50% predicted but <80% predicted, GOLD Stage III: FEV1 ≥30% predicted but <50% predicted, GOLD Stage IV: FEV1 <30% predicted.

Superficial SSI was defined according to the Infectious Diseases Society of America (IDSA) guidelines with the presence of: (1) purulent drainage, (2) positive culture of aseptically obtained fluid/tissue, (3) local signs and symptoms of pain or tenderness, swelling, and erythema after the incision is opened by the surgeon (unless culture negative), or (4) SSI diagnosis by the attending surgeon (24).

During both first and potential second DAIR procedures, the same surgical techniques were used, and joint fluid along with six periprosthetic tissue samples were collected for culturing. Empiric antibiotic therapy (flucloxacillin, 6g/day continuous IV infusion) began after tissue cultures were obtained. All modular parts (polyethylene liner and femoral head for THAs, polyethylene insert for TKAs) were removed, followed by careful debridement and joint irrigation. Pristine modular components were then inserted. Following surgery, the patient's vitals (including temperature) were recorded every six hours. Biochemical blood test (CRP, ESR, Leukocytes) were analysed every 2-3 days. Antibiotic treatment was adjusted based on preliminary culture results in consultation with infectiologists and microbiologists. PJI diagnosis was established according to the major Musculoskeletal Infection Society (MSIS) criteria, requiring at least two tissue cultures during DAIR showing growth of the same pathogen (25).

A second DAIR was performed if early infection control failed (<1 month after initial DAIR), indicated by rising or stagnant infection markers (CRP or leucocytosis), fever, local erythema, or prolonged wound drainage (>10 days). The instituted antibiotic treatment was continued during the second DAIR. The decision for a second DAIR was at the surgeon's discretion. Outpatient follow-up included routine check-ups at 2 and 6 weeks and 6 and 12 months. Regular CRP biochemical blood testing was conducted during these visits.

Statistical Analysis

Descriptive statistics were used to summarize the data. Two distinct groups were defined: one for cases with a single DAIR and another for those with a second DAIR (repeated DAIR). Standardized mean differences (SDM) were calculated. An SMD of less than 0.1 indicates balance because the SMD quantifies the difference in means between two groups relative to the pooled standard deviation. In the context of covariate balance assessment, a smaller SMD suggests that the distributions of the covariates are similar between groups. DAIR procedures were deemed failed if any form of revision surgery (one- or two-stage exchange arthroplasty, explantation, or other surgical procedure on the joint) occurred, or if suppressive antibiotic treatment was initiated. In the repeated DAIR group, a third DAIR procedure was also considered as treatment failure. All patients were retrospectively analysed

at least 2 years following index surgery. Kaplan-Meier survival analysis assessed failure rates using the aforementioned definitions for both single and repeated DAIR groups. Exploratory analyses investigated associations between patient, infection, or procedure-related characteristics for repeated DAIR failure, employing univariate and multivariate Cox regression. Evaluated characteristics included BMI, active smoking, polymicrobial infection, renal failure or COPD presence, implant age at first DAIR (joint age), time between first and second DAIR, bone cement usage during the index arthroplasty, and pre-DAIR CRP levels. For multivariable regression, patients with COPD and renal failure were categorized (COPD: none vs. GOLD 1 or higher; renal failure: G1 vs. G2 or higher). The proportional hazards assumption for our Cox regression model were assessed using Schoenfeld residuals. Schoenfeld tests did not indicate significant violations of the proportional hazards assumption for the models. Additionally, graphical inspection of Schoenfeld residuals over time showed no clear trends suggestive of non-proportionality.

RESULTS

124 patients were identified that underwent a DAIR procedure within 3 months after primary elective THA or TKA who met the major MSIS criteria for (early) PJI. Eighty-six (69.4%) cases underwent a single DAIR procedure that succeeded in achieving early infection control whereas 38 (30.6%) patients underwent repeated DAIR due to failure of achieving early infection control (Figure 1). No patients went directly from initial DAIR to revision surgery within 3 months.

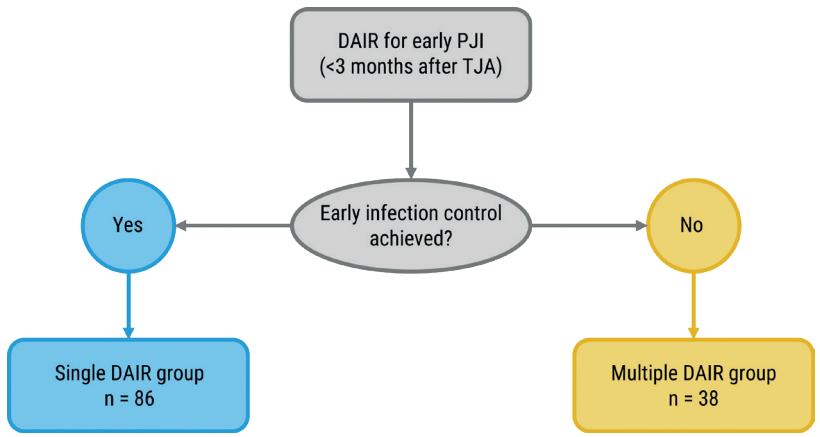

Figure 1: Flow-chart illustrating the workflow of the study.

The median time between index surgery and the first DAIR was 20 days (range 6 – 79), and the median time between the first and the repeated DAIR was 11 days (range 3 – 23). The identified causative pathogens are displayed in table 2. Staphylococcus aureus was the predominant causative pathogen (43.5% of cases in both groups combined) involved. The pathogens isolated during the repeated DAIR are displayed in table 2.

Table 2: Overview of data on the involved causative pathogens per group isolated during first DAIR (single DAIR or repeated DAIR).

	Culture results of first DAIR		**Culture results of repeated DAIR**
	Single DAIR n=86	**Repeated DAIR n=38**	**Repeated DAIR n=38**
Coagulase negative Staphylococcus (%)	17 (19.8)	8 (21.1)	6 (15.7)
Corynebacterium (%)	6 (7.0)	1 (2.6)	4 (10.5)
Enteric gramnegative (%)	7 (8.1)	7 (18.4)	7 (18.4)
Enterococcus (%)	7 (8.1)	2 (5.3)	5 (13.1)
Staphylococcus aureus (%)	39 (45.3)	15 (39.5)	8 (21.1)
Pseudomonas (%)	0 (0)	1 (2.6)	1 (2.6)
Streptococcus (%)	5 (5.8)	3 (7.9)	0 (0)
Other (%)	5 (5.8)	1 (2.6)	1 (2.6)
Polymicrobial (%)	32 (37.2)	16 (42.1)	8 (21.1)
Culture negative	-	-	15 (39.5)

In the third column the data on the pathogens isolated during repeated DAIR is displayed.

In the single DAIR and repeated DAIR groups, implant failure occurred 8 cases (9.9%; 95%CI 3.0% – 16.0%) and 8 cases (22.2%; 95%CI 7.3% – 34.7%) respectively after 2 years of follow-up (figure 2). No cases were identified that received suppressive antibiotics with implant retention.

Univariable Cox regression analyses did not identify any statistically significant associations between patient or procedure related factors and treatment failure of repeated DAIRs (table 3). Given the small sample size and low number of events, it was decided to not perform multivariable regression analysis.

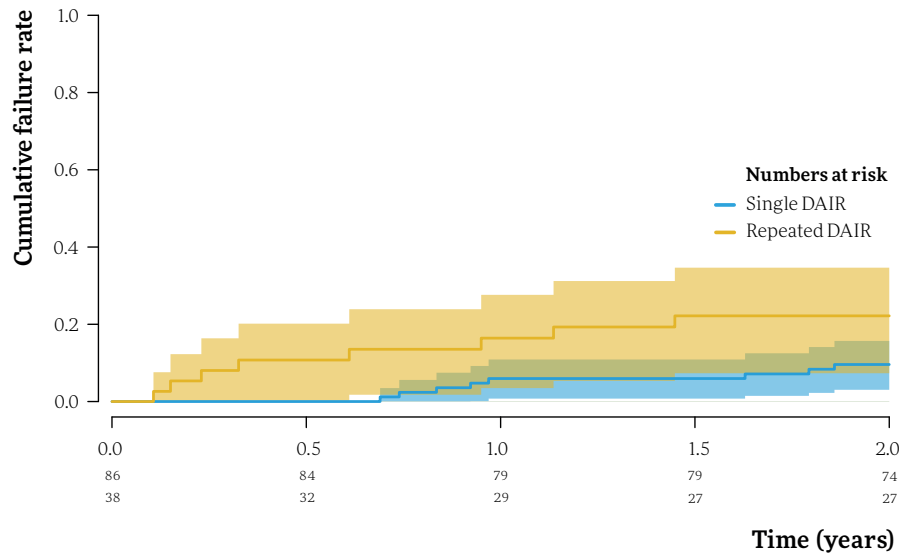

Figure 2: Kaplan Meier survival analysis illustrating the failure rate of the implants following early PJI (<3 months) after primary THA or TKA in the single (blue) and repeated (yellow) DAIR groups.

Table 3: Results of the univariable and multivariable Cox regression analysis for a potential association between treatment failure and several procedure, patient or infection characteristics, illustrated by the estimates of the hazard ratio.

	Univariable Cox regression		
	Hazard ratio	**95% CI**	**p-value**
BMI	1.02	0.90 - 1.15	0.80
Active smoker	1.33	0.32 - 5.58	0.69
Polymicrobial PJI	1.52	0.38 - 6.09	0.55
Renal failure (G1 vs. ≥G2)	0.239	0.05 - 1.19	0.08
COPD (No vs. ≥GOLD1)	0.647	0.08 - 5.27	0.68
Joint age	0.959	0.82 - 1.12	0.60
Time interval DAIR 1 – DAIR 2	0.966	0.82 - 1.14	0.67
Cemented fixation	0.560	0.14 - 2.24	0.41
CRP prior to first DAIR	1.00	0.99 - 1.01	0.39
CRP prior to repeated DAIR	1.00	0.99 - 1.01	0.67
Total knee arthroplasty	0.71	0.14 – 3.45	0.68
Positive cultures during repeated DAIR	5.67	0.69 - 46.2	0.10

These characteristics include: BMI (Body Mass Index), active smoking by the patient, polymicrobial PJI (Periprosthetic Joint Infection), renal failure (any degree), Chronic Obstructive Pulmonary Disease (COPD, of any degree), Joint age (time in days since initial arthroplasty up to the first DAIR), time interval between the first and second DAIR, Cemented fixation of the implant, CRP value prior to the first DAIR procedure and the CRP value prior to the second DAIR procedure. The estimate is an estimation of the hazard ratio (HR).

DISCUSSION

In this study a failure rate of 22.2% (95%CI 7.3% – 34.7%) for a repeated DAIR procedure was found versus 9.9% (95%CI 3.0% – 16.0%) in a group of patients where only a single DAIR procedure was deemed necessary for patients with an early PJI of a primary THA or TKA. These findings suggest that a repeated DAIR procedure could still be a viable treatment option in this particular context (primary THA/TKA, early PJI and failure of early infection control) since more than 75% of repeated DAIR procedures were able to prevent implant removal.

Repeated DAIR for early PJI treatment remains controversial. Vilchez et al. found that needing a second debridement was linked to failure of implant retention due to persistent PJI (13). This was supported by a large multicentre study of S. aureus PJI (n=345), where a second debridement was an independent risk factor for failure (14). Urish et al. showed that 109 of 216 patients who underwent DAIR after TKA required

additional procedures, with over 70% of those who had repeated DAIR ultimately failing (15). Another study on 64 patients with early PJI (<3 months) revealed a 61.5% failure rate for the 39 patients who underwent DAIR, all of whom subsequently required a second DAIR without success (16).

Conversely, several studies found no association between repeated DAIR and poor outcomes (8, 17, 18), suggesting it may be a viable option. However, available studies on repeated DAIR are limited, heterogeneous, and yield conflicting conclusions. Consequently, the international consensus on orthopaedic infections recommends considering implant removal after a failed first DAIR (12), citing that literature generally shows a second DAIR only has an equivalent success rate compared to the initial procedure. However, following the previously mentioned consensus meeting more favourable results of a repeated DAIR have been reported. These include the study by Wouthuyzen-Bakker et al. that demonstrated that a second DAIR had a low failure rate and that therefore, a second DAIR should not be discarded in acute PJIs (21). In addition, a recent retrospective multi-center study by Auñón et al. demonstrated that a second DAIR can achieve a 83% success rate in selected patients (22).

Based on both the results of the latter and this study and we recognize a lower success rate in cases where early control of PJI is not achieved however we would like to argue against a low threshold for the removal of implants after failure of early infection control with a single DAIR. Most of the studies, on which the recommendation of the consensus meeting is based, contain varying indications for DAIR (including late (hematogenous) infections and infections following revision TJA). These heterogeneous patient, procedure and infection characteristics may have influenced treatment outcomes significantly throughout different studies explaining the wide range in reported success rates. In contrast, this study describes a relatively homogeneous cohort of patients, consisting of solely early PJI (no late or hematogenous PJI) following elective primary TKA and THA (no revision surgery). Furthermore, the DAIR procedure was standardized including mobile bearing exchange and a clear indication for secondary DAIR (failure of early infection control within one month) was defined. As such, the results of this study seem to reflect the more favourable results of a repeated DAIR encountered in the literature (8, 17-19, 21, 22, 26). From this perspective a repeated DAIR may yet have a role in the specific circumstances of: Primary TKA or THA with early PJI (<3 months of implantation) and failure of early infection control (<1 month after initial DAIR).

In justifying whether the chances of success may still warrant a repeated DAIR, one also has to take into account the consequences of a single DAIR only approach. This approach may lead to an increase in implant removals in case of failure of early

control of PJI after a single DAIR procedure. Implant removals may go hand in hand with increased patient morbidity and complications.

In our opinion, the success rate of a repeated DAIR is only part of the puzzle in clinical decision making on whether or not to give it a chance. This study clearly indicates that chances of successful PJI control decrease when repeated DAIR is necessary. Still, a rather low threshold towards implant removal after failed single DAIR is not always without profound consequences for the patient. Such a decision should not be made lightly. The pros and cons regarding the choice for either a repeated DAIR procedure or implant removal will have to be weighed for each individual patient. Patient specific factors like bone stock and implant fixation, antibiotic susceptibility of the responsible pathogen, options for one-stage revision and patient comorbidities have to be taken into account.

Tools able to predict failure of repeated DAIR would greatly aid improvement in tailored patient specific clinical decision making. Previous studies have been able to identify risk factors associated with failure of initial DAIR procedures, including: time to (first) DAIR, liver cirrhosis, renal failure, use of bone cement during primary TJA and the CRP levels prior to DAIR (27, 28). These predictors most likely would also apply to a repeated DAIR procedure. In addition, few other studies have aimed to identify risk factors for failure of a repeated DAIR. Factors identified include non-specialized surgical teams in the first DAIR, non-exchange of mobile components, polymicrobial infections, antibiotic resistance, positive cultures during the second DAIR, chronic renal insufficiency and the time interval between DAIRs (20-22). Due to the small sample size and low number of events, it was decided to not perform multivariable regression analysis.

Our analysis is primarily exploratory, aimed at exploring hypotheses rather than drawing definitive conclusions. Based on the previous studies, one should be wary of failure when considering a repeated DAIR in case of patients with polymicrobial PJI, multi-resistant pathogens, chronic renal failure. In addition, there are recognized pathogens that are classified as more or less troublesome in the context of PJI. This distinction may influence the success rate of repeated DAIR. In the case of more resistant pathogens, such as Methicillin-resistant Staphylococcus aureus (MRSA), Enterococcus faecium, and Pseudomonas aeruginosa, a more cautious approach may be warranted regarding repeated DAIR (14, 29). Unfortunately, this study is inadequately powered to provide specific recommendations on this topic.

There is no data to support a clear cut-off point regarding a unacceptable time interval between first and second DAIR. However, the authors would advise caution with repeated DAIR more than a month after the first DAIR.

Future studies and potential meta-analyses, with a larger number of patients, may provide further tools to provide more specific recommendations on when to refrain from a repeated DAIR procedure in this context.

Limitations

This study, like others on this topic, has several limitations, including its retrospective nature and a relatively small cohort size, which may limit statistical analysis. It was underpowered to identify patient, procedure, or infection-related factors significantly associated with treatment failure. Additionally, the threshold for repeated DAIR may be lower than in other studies, potentially contributing to the relatively favourable outcomes observed. However, one could consider this consequential to our treatment strategy.

Finally, although guidelines exist for performing repeated DAIR, the decision for the go-ahead was ultimately made by various surgeons, possibly leading to differing treatment choices. However, second DAIRs are routinely performed in our hospital and progressing with complete revision or explant surgery after DAIR is extraordinary in our practice. Still, this surgeons' discretion could certainly influence the timing and potential threshold of the second DAIR. Nonetheless, this variability may accurately reflect everyday clinical practice.

Conclusion

In a group of patients with repeated DAIR the chances of failure of PJI control were higher than for patients where only single DAIR was necessary. Still, a success rate of more than 75% warrants its role in the treatment of failed early PJI control (< 1 month after initial DAIR) following a initial DAIR. Tailored decision making (considering all the relevant factors including implant revisability, options for one stage revision, patient comorbidity and pathogen antibiotic susceptibility) should be made on whether to proceed either with a repeated DAIR or with revision surgery. Future studies on larger patient cohorts will potentially allow further discern between favourable and unfavourable patients regarding the selection for repeated DAIR procedures.

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Competing interests

The authors declare that they have no conflict of interest.

Ethical statement

Ethical approval for this study was obtained from the local institutional review board (study number: 2019-1398).

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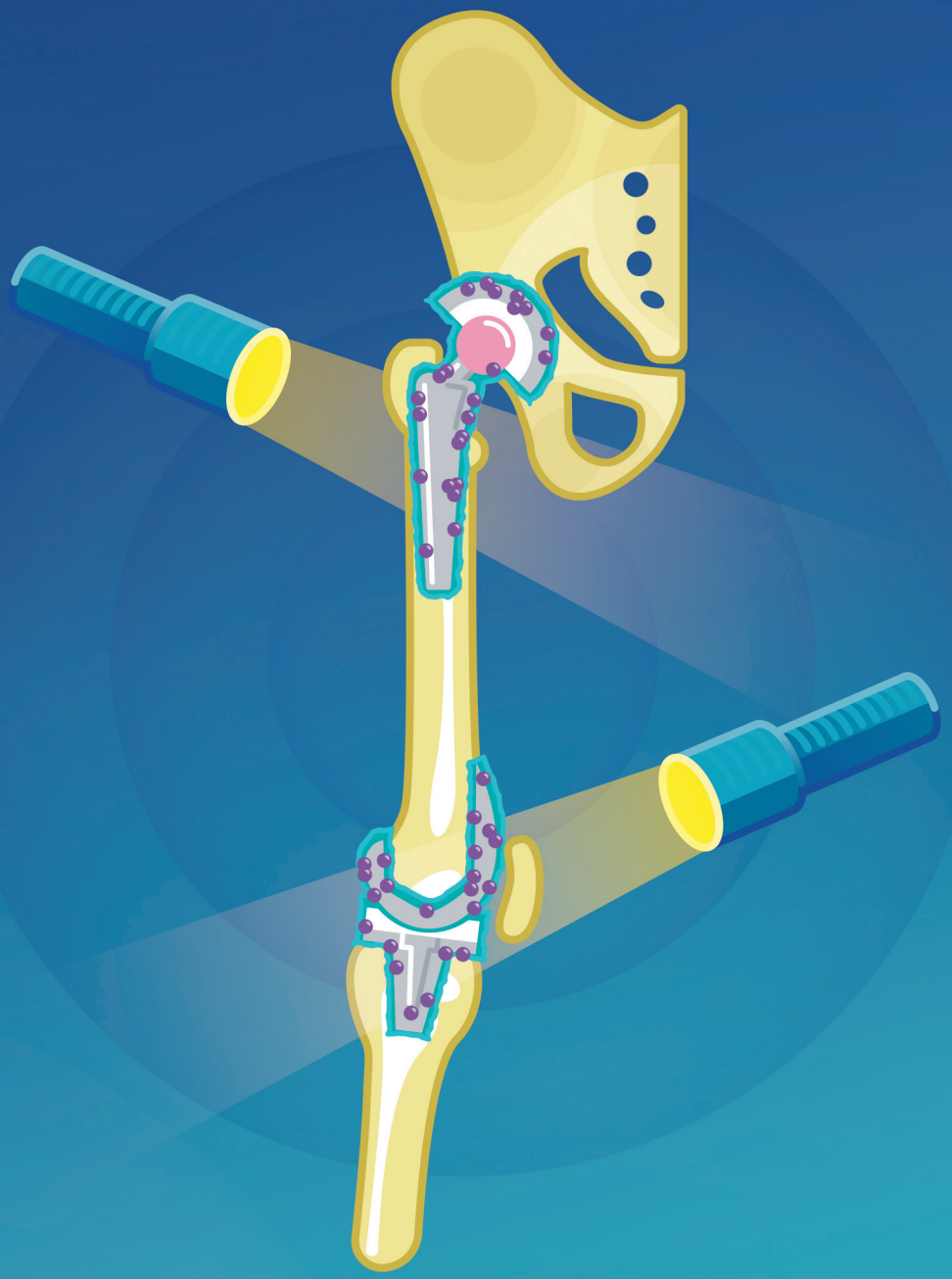

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Summary, general discussion and future recommendations

A periprosthetic joint infection (PJI) remains a severe complication following total joint arthroplasty (TJA). It is the leading cause for revision in primary total knee arthroplasty (TKA) and the third most common reason for revision of primary total hip arthroplasty (THA). With the growing number of THAs and TKAs performed each year due to an aging population and the rising prevalence of osteoarthritis, partly driven by comorbidities like obesity, the incidence of PJI is likely to increase in the future. Therefore, optimizing primary THA and TKA procedures to prevent PJI should be a top priority. Effective strategies focusing on prevention combined with improved diagnostics and treatment of an infection, play a pivotal role in mitigating this complication. Therefore, this thesis aimed to enhance the understanding of periprosthetic joint infection in total joint arthroplasty and providing insights and recommendations on its prevention, diagnosis, and treatment.

The following section of this thesis will summarize and discuss the investigated multifaceted aspects of PJI. At the end, also future recommendations will be stated. By delving into these critical aspects of PJI management, we aim to contribute valuable insights to the ongoing efforts to combat periprosthetic joint infection and improve the overall success and longevity of joint arthroplasty procedures.

PART I – PREVENTION

Hypothermia

Various studies have documented the harmful consequences of perioperative hypothermia on treatment outcomes and complication rates. As stated before, even slight perioperative hypothermia can elevate the likelihood of post-operative complications, such as increased mortality, sepsis, stroke, and surgical site infections (1). These effects are significant; a mere 1.9°C drop in core temperature can triple the risk of surgical site infections (SSI) and extend hospital stays by 20% (2). Despite these findings, the link between hypothermia and periprosthetic joint infection (PJI) remains undefined. In **Chapter 2**, we studied the potential relationship between perioperative hypothermia and the risk of PJI. The objectives of this study in the context of total hip and knee arthroplasty were:

1. Is there an association between hypothermia and PJI?
2. Is the incidence of hypothermia subject to change over time?

From January 2011 to December 2014, all patients undergoing elective primary unilateral total knee or hip arthroplasty for osteoarthritis were included. Standardized core temperature measurements were implemented following a previous study that identified a high incidence of intraoperative hypothermia (3).

Mild hypothermia was defined as a core temperature between 35 and 36°C, whereas severe hypothermia was defined as a core temperature below 35°C. Potential predisposing factors for hypothermia such as age, BMI, gender, type of arthroplasty surgery, anesthesia type, operation duration, blood loss, and surgery date were analyzed.

The incidence of PJI was 1.0% in hypothermic patients versus 1.9% in normothermic patients. This provided a non-significant (p=0.27) relative risk ratio of 0.52. This is not in line with findings in other surgical fields that suggested an increased risk of infection in general (1, 4). This discrepancy could be due to several factors. Perhaps only severe hypothermia (and not mild hypothermia) culminates into an increased PJI risk. An alternative explanation could be that in patients at a greater risk of PJI already more attention is given to the prevention of hypothermia. Furthermore, other factors could be more influential in the development of PJI. For example: a higher BMI is associated with a higher core temperature but also leads to a higher risk of PJI (5).

Finally, despite a considerable patient cohort, our study lacked the power to detect a statistically significant difference at a 0.05 threshold. This is probably related to the low incidence of PJI in general, as previously mentioned.

Interestingly, our study found a decrease in hypothermia rates over the study period. It was observed that the occurrence of mild hypothermia declined steadily during the study timeframe, reaching a plateau after two years. The reduction in hypothermia rates is likely due to increased awareness among involved personnel in both the ward and operating room, coupled with pre-operative warming measures. The overall incidence of hypothermia in primary total knee or hip arthroplasty procedures in this study was at 11.7%, a substantial drop from the 26.7% identified in the previous study in the same hospital (3).

Nasal colonization of Staphylococcus aureus

Staphylococcus aureus has been recognized as the primary microorganism responsible for surgical site infections (SSI), with nasal carriage of this bacterium being a significant risk factor for SSI development (6). Reducing nasal Staphylococcus aureus carriership by a 5 day protocol using mupirocin (patients apply a small amount of mupirocin nasal ointment twice a day inside each nostril using a clean finger or cotton swab) has shown efficacy in decreasing SSI rates across various surgical procedures (7). However, it is not clear whether this approach effectively reduces actual PJIs after primary total hip- or knee arthroplasty. Consequently, the effectiveness of prevalent and expensive screening and eradication programs in the context of total

knee arthroplasty (TKA) and total hip arthroplasty (THA) remains a topic of debate. In **Chapter 3**, we assessed the effectiveness of a preoperative *Staphylococcus aureus* screening and eradication protocol in lowering early PJI occurrences. This study aimed to assess a preoperative *Staphylococcus aureus* screening and eradication protocol in 2 aspects:

1. Is *Staphylococcus aureus* screening and eradication effective at reducing the incidence of early overall PJI?
2. Does *Staphylococcus aureus* screening and eradication by mupirocin reduce *Staphylococcus aureus* induced early PJI?

A retrospective study was conducted on all primary total hip arthroplasties (THA) and total knee arthroplasties (TKA) performed between January 2006 and April 2018 to assess early PJI rates. Data on demographics, PJI risk factors (ASA classification, Body Mass Index, smoking, diabetes) and implant types were gathered. In October 2010, a preoperative screening and eradication protocol targeting nasal colonization of Staphylococcus aureus was introduced in the Rijnstate hospital in Arnhem, the Netherlands. The incidence of early PJI was compared before and after the implementation of this protocol. Inverse probability weighting was utilized to balance covariates across patient and treatment groups, and weighted univariable logistic regression was employed to analyze early PJI rates in both cohorts.

Pooled weighted univariable regression analysis demonstrated no statistically significant differences regarding the risk of early PJI between the screened group (1.3%) and the control group (1.7%) (OR: 0.78; 95%CI: 0.55 – 1.11; p = 0.18). The incidence of early PJI with *Staphylococcus aureus* among the causative pathogens was 0.6% in the screening group versus 1.1% in the control group (OR: 0.58; 95% CI: 0.36 – 0.92; p=0.02). The incidence of early PJI with involvement of pathogens other than SA was 0.9% in the screening group versus 0.8% in the control group (OR: 1.05; 95% CI: 0.65 – 1.71; p=0.82).

This study highlights a notable reduction in *Staphylococcus aureus* induced PJI without a statistically significant overall decrease in PJI incidence after the introduction of a *Staphylococcus aureus* screening and eradication protocol in a sizeable patient cohort.

It is important to consider both the identified statistical significance and the clinical relevance of the achieved PJI reduction and the associated costs. The substantial number of screenings required to attain the observed significant effect should not be disregarded.

Despite adequate screening of *Staphylococcus aureus* carriers, there is a notable concern regarding the technique's effectiveness, as a significant portion of carriers may go unidentified despite this detection method, and some patients may remain colonized even after undergoing the eradication treatment (8, 9). Alternatively, universal decolonization (treating all patients with nasal mupirocin without prior screening) has been proposed as a potentially more effective and cost-efficient approach in reducing early prosthetic joint infections (PJI) compared to a screening and selective decolonization strategy (10). However, a significant drawback of universal decolonization is the risk of fostering widespread mupirocin resistance due to the excessive treatment of 74% of patients (only 26% of patients were carriers of *Staphylococcus aureus*).

The findings of this study provide additional support for evaluating the true clinical benefits of widespread adoption of *Staphylococcus aureus* screening and decolonization in elective total joint arthroplasty (TJA). Especially in the light of the costly and resource-intensive aspects of these protocols, the clinical benefit should not be overestimated.

Hardware removal and concomitant total hip arthroplasty

A systematic review highlighted an elevated PJI risk following THA in individuals with a history of prior internal fixation for a proximal femoral fracture (11). Nonetheless, recent studies have contradicted this, indicating no increased risk of early PJI after salvage THA (12-14). Consequently, conflicting perspectives persist in the literature regarding the potentially increased risk of PJI associated with THA and concomitant hardware removal. Therefore, uncertainty remains regarding whether a one-stage approach involving both implant removal and subsequent hip arthroplasty or a two-stage procedure with a time gap in between procedures is more advisable. **Chapter 4** aimed to investigate the early PJI incidence in THA following hardware removal and offer a comparative analysis of early PJI rates between single-stage and two-stage THA coupled with hardware removal. In this context, the main research questions were:

1. What is the incidence of early PJI following (salvage) THA following hardware removal?
2. What are the incidences of early PJI following either single-stage or two-stage THA with hardware removal.

A review was performed on all patients who underwent THA following hardware removal after previous osteosynthesis between January 2006 and March 2018 to assess the occurrence of early prosthetic joint infection (PJI). Known risk factors for

PJI at the time of surgery were analyzed, and the incidence of early PJI was compared between one-stage and two-stage THA procedures involving hardware removal.

A total of 145 patients underwent THA along with hardware removal, consisting of 52 patients in the two-stage surgery group and 93 patients in the single-stage surgery group. There were no statistically significant differences between the two groups concerning pre-operative hemoglobin levels, the time interval between internal fixation and THA, the use of antibiotic-loaded cement during arthroplasty, BMI, and ASA classification. The overall incidence of early prosthetic joint infection (PJI) was found to be 6.9 percent which hints at an increased risk of PJI following previous osteosynthesis. The incidence of PJI was 8.6 percent in the single-stage group compared to 3.8 percent in the two-stage group (p=0.234).

These results indicate a potentially increased risk of PJI following THA with concomitant hardware removal. The noticeable difference between our findings and those of other recent studies may be due to variations in patient populations as our research was carried out in a large general teaching hospital rather than a tertiary orthopaedic referral centre. Also, the percentage of patients with ASA classifications 3 and 4 in our study is significantly higher compared to other studies (14) which potentially increases the risk of PJI in this study population.

The decision between performing hardware removal concurrently with total hip arthroplasty (THA) or as a separate procedure remains a topic of debate, with insufficient high-level evidence to support either approach. In our study, the 3.8 percent incidence of early PJI observed after the two-stage procedure may indicate its superiority over the one-stage method; however, this difference was not statistically significant due to the limited number of PJI cases. Regarding confounding factors, only two recognized risk factors for PJI showed significant differences between the groups: surgery duration and patient age, while BMI and ASA classification did not demonstrate any effect. The surgery duration was longer for the single-stage group, as expected, due to the need for additional surgical procedures. Still, care must be taken when drawing conclusions on this subject since the decision to use either a one-stage or two-stage procedure was not standardized. This introduces potential confounding by indication and therefore selection bias. This tendency has led to a preference for one-stage procedures in relatively fragile patients presenting with severe and acute pain where a two stage approach would be less feasible.

As aforementioned, regardless whether a single-stage or two-stage procedure was performed, a high incidence of PJI was observed. Single-stage surgery may be associated with a higher risk of PJI. We recommend opting for a two-stage surgical

procedure for hardware removal and THA in patients who are likely to tolerate this approach.

Type of anesthesia

Despite growing awareness of the significance of preventing PJI, the influence of procedure-related factors, such as the type of anesthesia, remains unclear (15). Interestingly, the idea that anesthesia might affect the immune response was proposed as early as 1903 (16). Several recent studies have indicated that spinal anesthesia may lower the risk of surgical site infections (SSI) when compared to general anesthesia in THA and TKA (17, 18). However, other research has found no association between the type of anesthesia and SSI (19-21). Notably, no studies have evaluated the role of anesthesia during THA and TKA with clearly defined PJI criteria. **Chapter 5** investigates the relationship between the type of anesthesia (spinal or general) and early PJI following THA or TKA in a large-scale observational cohort study. One main research question was formulated:

1. Is there an association between the type of anesthesia (i.e. spinal or general) and PJI incidence following elective THA or TKA?

All consecutive patients who underwent elective primary unilateral TKA or THA between January 2014 and December 2017 in the Rijnstate hospital (Arnhem, the Netherlands) were included in the study. Patients were excluded if the indication for surgery was femoral fractures or if they had previously undergone osteosynthesis or hardware removal on the affected joint. To account for confounding by indication, propensity score-matched univariable logistic regression analysis was employed.

Early PJI occurred in 1.7% of the general anesthesia group and in 0.8% of the spinal anesthesia group. The multivariable logistic regression model indicated an odds ratio of 2.0 (95% CI 1.0 - 3.7) for PJI following general anesthesia compared to propensity score-matched patients who underwent spinal anesthesia.

These results indicate an increased risk of early PJI following TJA under general anesthesia. The mechanism by which general anesthesia may elevate the risk of infection, or how spinal anesthesia may reduce it, remains unclear. One proposed explanation is that spinal anesthesia may enhance tissue oxygenation due to decreased postoperative pain and its vasodilatory effects (22). Along with improved tissue oxygenation, neuraxial anesthesia is in general associated with lower blood loss and decreased incidence of hyperglycemia, both of which can have immunosuppressive effects (23, 24).

In contrast, certain anesthetic agents used in general anesthesia can impair leukocyte chemotactic migration, phagocytosis, lymphocyte function and even promote bacterial growth in cases of contamination (16). Furthermore, studies comparing general and spinal anesthesia found that the immunosuppressive effects associated with spinal anesthesia were minimal (25).

Concluding, this study suggests a possible link between general anesthesia and PJI. Further large-scale studies are needed to clarify this clinically significant relationship.

PART II – DIAGNOSIS

When preventive measures seem to have failed, accurate diagnosis of PJI is essential for obvious reasons. First and foremost, timely and precise identification of PJI is crucial for initiating appropriate and effective treatment strategies, which may include surgical intervention, antibiotic therapy, or even revision arthroplasty. An incorrect or delayed diagnosis can lead to inappropriate treatment, worsening the patient's condition, prolonging suffering, and potentially resulting in catastrophic consequences, including loss of limb function or systemic infection. Secondly, achieving an accurate diagnosis ensures proper differentiation between PJI and other postoperative complications, such as aseptic loosening or inflammatory responses unrelated to infection. Misdiagnosis can lead to unnecessary or harmful interventions, increasing morbidity and healthcare costs associated with prolonged hospital stays, additional surgeries or ineffective treatments.

Tissue cultures are considered the gold standard for diagnosing PJI because they directly identify the presence of bacteria or other pathogens in the tissues surrounding the prosthetic joint. This provides definitive evidence of infection. However, acquiring tissue cultures prior to the final surgery necessitates an invasive procedure, which can be inconvenient for both patients and clinicians, as the appropriate surgical treatment remains uncertain due to the absence of a definitive diagnosis. Furthermore, additional surgery carries inherent risks, including infection, bleeding, and anesthesia-related complications. A significant drawback of taking per-operative cultures at the time of the revision procedure is the delay in time until the culture results are available. Tissue cultures often take several days to grow, with some bacteria requiring even longer incubation periods up to 2 weeks. Therefore, a reliable and quick test to identify PJI prior or during surgery would greatly aid clinical decision making.

The Synovasure® lateral flow test for diagnosing PJI

Diagnosing PJI and initiating the appropriate surgical treatment is currently not always feasible. Unfortunately, there is nowadays no reliable method to determine intra-operatively whether an infection is present. To address this issue, the Musculoskeletal Infection Society (MSIS) has established criteria to guide decision-making in the evaluation of suspected PJIs (26). Nonetheless, this evaluation process is complicated by the lack of a standardized test.

As a result, a rapid and reliable test capable of distinguishing intraoperatively between infected and uninfected prostheses would be invaluable. One key indicator for establishing PJI intra-operatively, according to the MSIS, is the presence of elevated levels of α-defensin in the synovial fluid of the prosthetic joint. To facilitate more timely decision-making between "septic" and "aseptic" surgical treatments, a rapid test for α-defensin in synovial fluid has been developed. **Chapter 6** evaluates the effectiveness of this test. The main research questions were:

1. What is the sensitivity of the Synovasure® lateral flow test for diagnosing PJI?
2. Are false-negative results associated with the presence of metallosis?

Thirty-seven patients that underwent revision surgery for suspected early aseptic loosening (<3 years after primary arthroplasty) were included in a prospective study design. The Synovasure® test was used intraoperatively (to confirm the aseptic nature of the implant loosening) and 6 tissue-cultures were obtained in all cases. Patients were excluded with a preoperatively confirmed PJI, acute revisions (<90 days after primary arthroplasty) and cases with malpositioning, wear or instability of the prosthesis.

Five out of 37 included patients were ultimately diagnosed with PJI based on the growth of microorganisms in the obtained tissue cultures. Only one out of these 5 patients had a positive Synovasure® test. Thus, there were 1 true-positive Synovasure test, and 4 false-negative Synovasure tests yielding a sensitivity of 20%. No false-positive Synovasure tests were observed, even in the presence of metallosis which was observed in a single case (which yielded a negative Synovasure test).

Three earlier studies reported the Synovasure® test's sensitivity ranging from 67% to 97% and its specificity between 93% and 96% for diagnosing PJI (27-29). However, the diverse patient populations in these studies, which included various indications for revision surgery, complicate the interpretation and comparison of these values. Unlike these previous studies, our research focused specifically on a uniform subgroup of patients undergoing revision surgery for suspected early aseptic loosening.

These findings suggest that the Synovasure lateral flow test offers limited additional value for intraoperative exclusion of PJI caused by low virulent microorganisms in this homogeneous subgroup of patients experiencing suspected early aseptic failures of THA and TKA. No statements could be made about the role of metallosis (n = 1) in terms of test reliability.

PART III – TREATMENT

Empiric antibiotic treatment

Early debridement, antibiotics and implant retention is the mainstay of adequate treatment of early acute PJI. Several patient- and procedure related factors have been suggested to improve the treatment outcomes of debridement, antibiotics, and implant retention (DAIR). The appropriate choice of antibiotic treatment is of key importance for successful treatment. Some studies have indicated an association between ineffective empiric antibiotic therapy and treatment failure (30, 31). However, the obtained tissue cultures from DAIR surgery need a few days (often 5-7 days) before the causative pathogen and optimal antibiotic can be identified. Until the causative pathogen is identified antibiotics have to be started empirically. Unfortunately, the optimal empiric antibiotic treatment for PJI remains a relatively underexplored area in the current literature. **Chapter 7** explores the common pathogens involved in early PJI and their antibiotic susceptibilities to gain further insights into the optimal empirical antibiotic therapy following DAIR.

All consecutive patients who underwent DAIR within three months following primary unilateral TKA or THA between January 2011 and December 2018 in the Rijnstate hospital (Arnhem, the Netherlands) were retrospectively identified from the hospital's electronic health records. Information on the causative pathogens, antimicrobial susceptibility, and the number of postoperative days until cultures showed bacterial growth was gathered.

A total of 111 early PJIs were identified, with 65 (59%) being monomicrobial and 46 (41%) polymicrobial. Among the isolated pathogens, *Staphylococcus aureus* was the most prevalent pathogen, being isolated in 53 cases. Seventy-two percent of the PJIs were susceptible to vancomycin, which could be increased to approximately 90% by incorporating the coverage for gram-negative bacteria. Bacterial growth was detected in 98% of cases by the fifth postoperative day, and all gram-negative bacteria showed positive tissue cultures by the fourth postoperative day.

Even in the absence of methicillin resistant *Staphylococcus aureus* MRSA, cumulative antimicrobial susceptibility indicated that vancomycin yielded the highest coverage. Additionally, 41% of the PJIs were polymicrobial, which emphasizes the necessity of broad-spectrum empiric antibiotic therapy. The identification of Staphylococcus aureus and coagulase-negative staphylococci (CNS) as the most common pathogens, along with the range of other isolated pathogens in this study, aligns with findings from several previous studies conducted in various geographic regions that have examined the microbiology of PJI (32-37). Several recommendations on the most appropriate empirical antibiotic treatment for PJI have been formulated in the literature. However, the generalizability of these recommendations to regions with low incidences of MRSA is therefore questionable (38). In this study, no infections with MRSA were detected, yet vancomycin demonstrated the highest coverage among all analyzed mono-therapeutic antibiotic regimens. This coverage could be enhanced by incorporating ceftriaxone or ciprofloxacin to the treatment regime to address gram-negative pathogens. However, it is important to consider the significant drawbacks of vancomycin, such as its higher toxicity compared to beta-lactam antibiotics, the need for monitoring blood levels (and thereby increased costs and labor intensity), reduced effectiveness against methicillin-sensitive Staphylococcus aureus and its suboptimal activity against biofilms (39-41). The latter is important, since it implies that high coverage does not necessarily imply high efficacy.

Based on this study, empiric treatment of gram negative pathogens can be safely terminated on day 4 in case of no growth of these pathogens at that point in time.

Ninety-eight percent of all cultures showed bacterial growth by the fifth day. Given this finding and the fact that 30% of primary DAIR procedures were excluded from this study due to the absence of PJI, there may be circumstances where discontinuing empirical antibiotics could be justified in cases with a lower likelihood of infection. However, it is essential to approach the decision to stop antibiotics in patients who have already received preoperative antibiotic treatment with caution.

Repeated DAIR for failure of early infection control

Treatment success rates of DAIR, which can be as low as 26%, suggest that experiencing treatment failure after DAIR is not unusual (42-50). If a primary DAIR procedure fails, the surgeon must decide between repeating the DAIR procedure or moving forward with either a one-stage or two-stage revision of the implant. While a repeated DAIR procedure may be considered, this approach remains highly controversial (51). However, as a repeated DAIR procedure may be able to prevent (far more extensive) revision surgery, it may be of great value. In **Chapter 8**, the effectiveness of repeated DAIR procedure for early failure of infection control was assessed. This study consisted of 2 main objectives:

1. Identify the failure rate of a repeated DAIR procedure for unsuccessful early infection control in early PJI.
2. Compare these results to the failure rate of a single DAIR with adequate early infection control.

All DAIR procedures executed in the Rijnstate hospital (Arnhem, the Netherlands) for early periprosthetic joint infection following primary THA or TKA from 2010 to 2019 were reviewed retrospectively. In this cohort, a failure of early infection control (within one month post-DAIR) led to a subsequent DAIR procedure. Follow-up assessments were carried out for all cases for up to two years after surgery. Kaplan-Meier survival analysis was utilized for both single and repeated DAIR groups, while Cox regression analyses were conducted to identify risk factors associated with eventual implant failure following repeated DAIR.

A total of 124 cases of early PJIs were analyzed. Single DAIR procedures successfully achieved adequate infection control in 69.4% (n = 86) of the cases, while 30.6% (n = 38) required a repeated DAIR. After two years, implant removal was performed in 9.6% for the single DAIR group and in 22.2% for the repeated DAIR group. There were no statistically significant associations found between the failure of repeated DAIR and its potential risk factors.

Repeated DAIR for treatment of early PJI remains a controversial treatment modality. Available studies on repeated DAIR are scarce, heterogeneous and represent contradictory conclusions. However, our findings suggest that a repeated DAIR procedure could be a viable treatment option in this particular context (primary THA/TKA, early PJI and failure of early infection control) since more than 75% of repeated DAIR procedures were able to avoid implant removal. In case of repeated DAIR the chances of failure of PJI control were higher than for patients where only single DAIR was necessary. Still, a success rate of more than 75% warrants its consideration in the treatment of failed early PJI control within a month of initial DAIR.

Many of the previously referenced studies include a variety of indications for DAIR, such as late (hematogenous) infections and infections following revision TJA. This diversity in patient profiles, procedural approaches, and infection types may have significantly impacted treatment outcomes across different studies, contributing to the wide range of reported success rates. In contrast, the current study focuses on a relatively uniform cohort of patients, consisting exclusively of early PJIs following elective primary TKA and THA. On the other hand, the threshold for performing repeated DAIR may be lower compared to other studies or institutions, potentially

contributing to the relatively positive outcomes observed in this study. Nevertheless, this approach can be regarded as an integral part of our treatment strategy, which appears to achieve favorable results when employing repeated DAIR procedures.

A well-considered decision, taking into account factors such as implant revisability, options for single-stage revision, patient comorbidities, and pathogen antibiotic susceptibility, should determine whether to proceed with repeated DAIR or revision surgery.

CONCLUSIONS, RECOMMENDATIONS AND FUTURE PERSPECTIVES

PJI imposes a substantial burden on both patients and societies due to its severe impact on health outcomes and healthcare costs. For patients, PJI can lead to prolonged pain, decreased mobility and a significant decline in the quality of life, often necessitating complex treatments, extended hospital stays and multiple surgeries. On a societal level, the increased demand for healthcare resources, including prolonged rehabilitation and follow-up care, as well as lost productivity due to recovery times, contributes to higher overall medical expenses and strains healthcare systems. The multifaceted challenges presented by PJI underscore the need for effective prevention, early diagnosis, and treatment strategies.

Throughout this thesis, each study has focused on at least one of these aspects of PJI, highlighting the significance of modifiable risk factors, innovative diagnostic techniques, and treatment modalities. By examining these elements in depth, we aim to contribute to the ongoing efforts to better manage PJI and ultimately improve the quality of care for patients undergoing joint replacement surgery. This has resulted in the following conclusions and recommendations for orthopedic practice:

1. Perioperative hypothermia does not seem directly related to PJI, but more extensive research is required to further assess this potential correlation. However, prevention of hypothermia remains advisable due to its tendency to cause adverse events.
2. A preoperative nasal Staphylococcus aureus screening test seems to have at best a limited effectiveness in the prevention of PJI.
3. Concomitant hardware removal during THA may be associated with an increased risk of PJI. If possible, a two stage procedure may be safer than a single stage procedure.
4. The incidence of PJI seems to be higher following TJA under general anesthesia than under spinal anesthesia. Therefore, spinal anesthesia seems to be preferable in TJA in this context.
5. In a case series of presumed aseptic revisions, an α-defensin lateral flow test had no additional value to intraoperatively rule out low-grade PJI.
6. Vancomycin combined with a gram-negative antibiotic agent yield the highest coverage of potential pathogens in early PJI.
7. Repeated DAIR may still be considered in case of failed early PJI control within a month of initial DAIR after primary THA/TKA.

In conclusion, while this thesis aimed to contribute with valuable insights into the prevention, diagnosis, and treatment of PJI, it is evident that many aspects of this complex condition remain unclear. The multifactorial nature of PJI necessitates continued exploration and rigorous research to further illuminate its underlying mechanisms and optimize clinical outcomes.

As mentioned previously, many aspects of PJI remain elusive and controversial. These (prevention, diagnosis and its treatment) include all the aspects assessed in this thesis. Future research on PJI should be prioritized to the fields in which it can have maximal impact. As is the case with any disease, prevention is better than cure. Effective prevention of PJI will halt its impact on patients and healthcare systems and eliminates the need for complex diagnostics and challenging treatments. Fewer PJIs translates to fewer revision surgeries, less patient suffering, and lower healthcare costs.

To reduce the incidence of infections following implantation procedures, it is essential to enhance staff discipline within the operating room. The Rijksinstituut voor Volksgezondheid en Milieu (RIVM) has emphasized this issue in the Netherlands since 2010, and it remains critical to remain vigilant regarding these modifiable factors moving forward. The key points are as follows:

1. Administer the most appropriate prophylactic antibiotic in the correct dosage and timely manner. Administering the antibiotic after the initiation of surgery decreases its effectiveness.
2. As previously mentioned, preventing hypothermia is crucial. Several measures should be implemented, and all personnel involved in the surgical environment must remain alert and attentive.
3. Scrub the surgical site meticulously; evidence suggests that performing the scrub twice is more effective than once. Subsequent actions should only commence after the skin has dried post-scrubbing, as the drying process is a vital component of the antimicrobial efficacy of iodine or chlorhexidine.

4. Minimize the number of staff present in the operating room to the necessary minimum and avoid unnecessary movements through theatre doors during surgery to limit potential contamination.

While these guidelines may appear straightforward, maintaining compliance with them consistently proves challenging. Continuous focus on these behavioral measures is essential for improving patient outcomes in the future.

Many modifiable risk factors for PJI have been identified that seem to increase the risk of PJI. However, there are still many controversies regarding the optimal strategy to "modify" these risk factors in an effort to optimize outcome. Still, it is vitally important to postpone surgery in patients that have an increased risk of PJI until the patient is optimized and as fit as possible for surgery. However, this is not straightforward. For instance, obesity is associated with a higher risk of PJI but there are many controversies around its role and management in the context of PJI. Weight loss counseling often fails to achieve sufficient weight reduction in most patients (52). While bariatric surgery has been explored as a method to reduce postoperative complications, its effectiveness remains controversial, with inconsistent evidence of diminished perioperative risk (52). One of the issues with bariatric surgery is that it usually leads to changes in dietary habits, which can result in deficiencies of essential nutrients, such as protein, vitamins (like A, C, and E), and minerals (like zinc). These nutrients are crucial for the healing process and can impair wound healing which is highly undesirable following orthopedic joint replacements. Hence, it can lead to a range of negative outcomes, including increased postoperative pain, longer recovery times, and of course PJI. These deficiencies can persist up to 2 years post bariatric surgery (53). Some researchers indicate that prior bariatric surgery may elevate the chances of perioperative blood transfusions, as well as increase the risk of revisions and infections in long-term follow-up (54). Perhaps the thickness of subcutaneous fat at the surgical site may be a more accurate predictor of complication risk than body mass index alone (52). Also, a proper assessment of a patient's nutritional status and the correction of nutritional deficiencies may be more important.

The issue of how to modify the modifiable patient related risk factor does not only apply to obesity. Other known risk factors also do increase the risk of PJI (e.g. diabetes mellitus, malnutrition), but there is much controversy on how to address these factors. Research aimed at elucidating effective management strategies or the mechanism through which they contribute to the increased risk of PJI would contribute greatly to the prevention of PJI.

Further research on optimizing nutritional status (in general) may significantly reduce the incidence of PJI following TJA because proper nutrition plays a critical role in supporting immune function and promoting wound healing. Nutritional deficiencies can impair the body's ability to fight infections and recover from surgery, increasing the risk of complications such as PJI. By identifying effective strategies for nutritional optimization before surgery, healthcare providers may potentially enhance patients' resilience against infections, leading to improved outcomes and reduced rates of PJI. Such research could ultimately contribute to safer surgical procedures.

The aforementioned options to optimize the patients for surgery is being implemented in the Netherlands in several hospitals through a foundation called Fit4Surgery. Fit4Surgery is an initiative in the Netherlands aimed at optimizing patients' physical and mental preparedness for surgical procedures. The program focuses on preoperative patient education and lifestyle enhancement, emphasizing the importance of physical fitness, nutritional improvement, and psychological well-being prior to surgery. By addressing these modifiable factors, Fit4Surgery seeks to enhance surgical outcomes and reduce the risk of postoperative complications.

The primary objectives of Fit4Surgery include the promotion of patient empowerment through personalized training programs, nutritional guidance, and psychological support. Through these interventions, the initiative advocates for the adoption of healthier behaviors that can lead to improved recovery times and overall health status. By implementing such comprehensive preoperative preparations, Fit4Surgery aims to contribute to the efficacy of surgical interventions and enhance the quality of care provided to patients in the healthcare system. I believe that programs like Fit4Surgery could be helpful in reducing complications like PJI.

Apart from optimizing the patient, there is also the possibility of optimizing the implant. Recent advancements in implant coatings designed to mitigate PJI have primarily focused on enhancing antimicrobial properties while ensuring biocompatibility. This includes the development of antimicrobial coatings incorporating metals such as silver, copper, or zinc, which offer controlled release to inhibit bacterial colonization. Additionally, antibiotic-releasing coatings enable the targeted delivery of high concentrations of antibiotics directly at the implant site, minimizing systemic exposure and effectively reducing infection risks. Moreover, polymeric coatings, such as antimicrobial polymers or hydrogels, can be applied to inhibit bacterial adhesion. Implementing these strategies may offer new avenues for creating more effective and durable solutions to reduce the incidence of PJI by preventing bacterial colonization and biofilm development on implant surfaces.

The question is whether it will ever be possible to completely prevent periprosthetic joint infections (PJI). This may be an unrealistic expectation, meaning there will always be a need for effective treatment of PJI. The biggest challenge often lies in differentiating between low-grade infections and aseptic implant failure, since each condition requires a distinct treatment approach. Unfortunately, there are currently no rapid, minimally invasive, or non-invasive tests available to reliably confirm or rule out low-grade infections. Future research aimed at potential serum- or synovial fluid based biomarkers to reliably distinguish the aseptic from the low-grade septic implant failures would greatly reduce the burden of PJI patients. It would allow patients to be treated accordingly, thereby minimizing the consequences of incorrect treatment.

A future perspective on improving PJI treatment might be the implementation of bacteriophages. Bacteriophage therapy has the ability to specifically target and lyse antibiotic-resistant bacteria that often complicate such infections. Phages may effectively penetrate and disrupt biofilms on implant surfaces, which are notoriously resistant to conventional antibiotic treatments. Additionally, this therapy may reduce the reliance on antibiotics, thereby minimizing the risks associated with antibiotic resistance and adverse effects. Although initial studies and compassionate use cases have reported positive outcomes, further clinical trials are necessary to establish standardized protocols and confirm the efficacy and safety of bacteriophage treatment in the management of PJI (55).

While future research may be able to identify factors that can enhance both the prevention, diagnosis and treatment of PJI, there are likely other methods to improve the care of patients with PJI. This may include centralizing the management of challenging cases in specialized centers. As mentioned in this thesis regularly, the incidence of PJI is low. This means that orthopedic surgeon do not encounter this issue frequently, let alone therapy-resistant cases or chronic PJI. Research suggests that better treatment outcomes may be achieved when care is provided by experienced centers (56). Therefore, the outcomes may be improved if challenging cases are managed in such specialized facilities, e.g. those that fail to achieve early infection control following initial DAIR. Another option could be to establish dedicated teams within each hospital that treats PJI, ensuring they receive additional training and specifically focused on PJI.

By establishing a foundation for future research, this work aims to inspire further studies that will enhance our understanding of PJI, ultimately leading to improved strategies for prevention and management. As we strive to refine our approaches to PJI, it is essential that the orthopedic community remains committed to ongoing research efforts to mitigate the impact of this threat to patients and healthcare systems.

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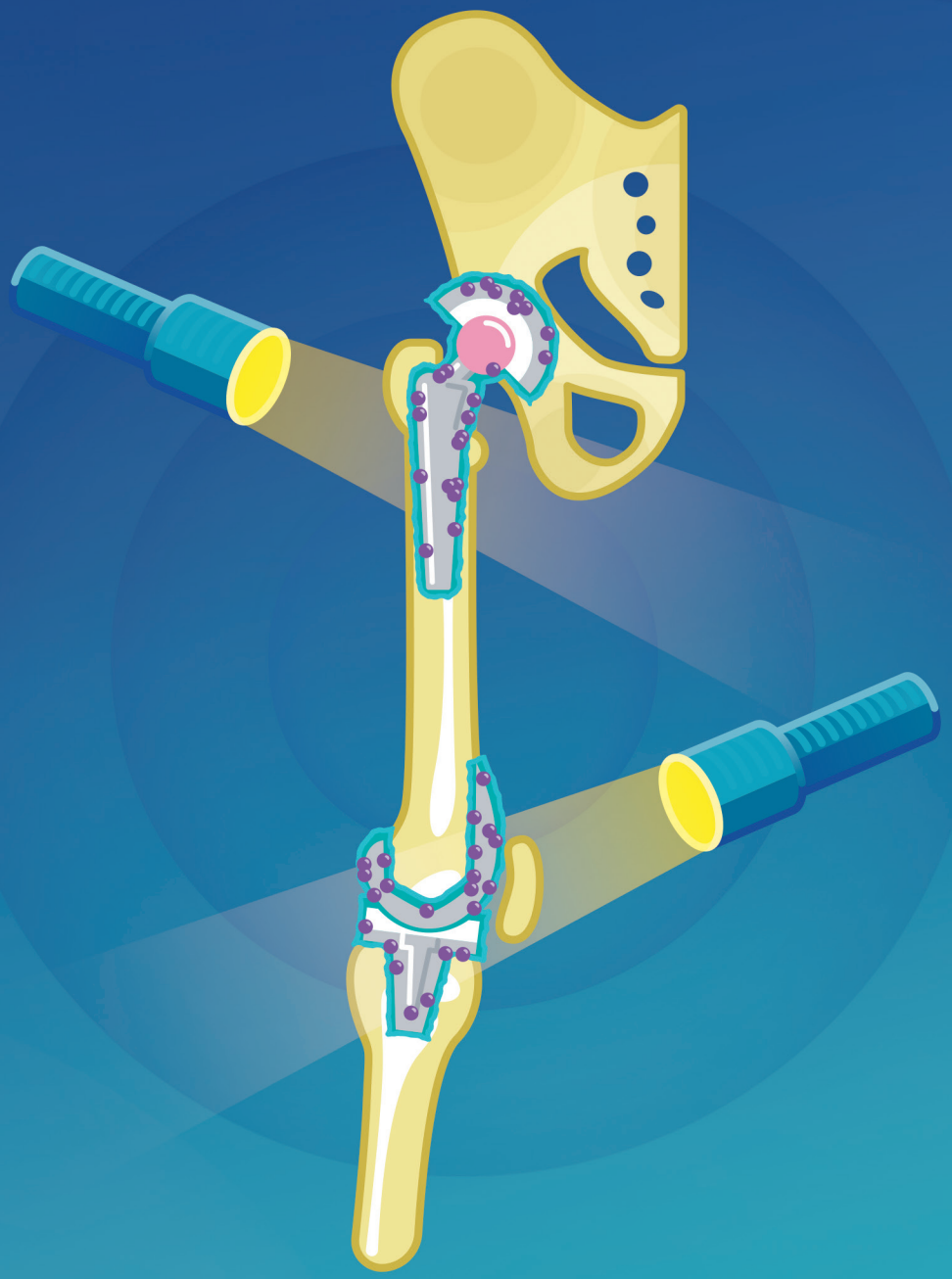


10

Nederlandse samenvatting en discussie

Een periprothetische gewrichtsinfectie (PGI) blijft een ernstige complicatie na een totale gewrichtsvervanging (TGV). Het is de belangrijkste reden voor revisie bij primaire totale knieprothesen (TKP) en de op twee na meest voorkomende reden voor revisie van primaire totale heupprothesen (THP). Door de toenemende vergrijzing en de stijgende prevalentie van artrose, mede veroorzaakt door co-morbiditeiten zoals obesitas, neemt het aantal THP- en TKP-ingrepen jaarlijks toe. Hierdoor zal ook het aantal PGI-gevallen in de toekomst waarschijnlijk stijgen. Daarom is het optimaliseren van primaire THP- en TKP-procedures om PGI te voorkomen van groot belang. Effectieve strategieën gericht op preventie, diagnose en behandeling spelen een cruciale rol bij het verminderen van deze complicatie. Dit proefschrift heeft als doel het begrip van periprothetische gewrichtsinfecties bij totale gewrichtsvervanging te vergroten en inzichten en aanbevelingen te bieden over de preventie, diagnose en behandeling van deze infecties.

In het volgende deel van dit proefschrift worden de verschillende onderzochte aspecten van PGI samengevat en besproken. Tot slot worden er ook aanbevelingen voor de toekomst gegeven. Door deze cruciale aspecten van PGI-management te analyseren, hopen we bij te dragen aan de lopende inspanningen om periprothetische gewrichtsinfecties te bestrijden en het succes en de duurzaamheid van gewrichtsvervangende ingrepen te verbeteren.

DEEL I – PREVENTIE

Hypothermie

In **Hoofdstuk 2** werd een mogelijk verband tussen perioperatieve hypothermie en het optreden van PGI's geanalyseerd. Verschillende eerdere studies beschrijven de mogelijke schadelijke gevolgen van perioperatieve hypothermie op de behandelresultaten. Zelfs milde hypothermie kan het risico op postoperatieve complicaties, zoals overlijden, sepsis, beroerte en postoperatieve wondinfecties, verhogen. Een daling van slechts 1,9°C in de kerntemperatuur zou het risico op infecties kunnen verdrievoudigen en het ziekenhuisverblijf van een patiënt met 20% kunnen verlengen. Ondanks deze bevindingen is een mogelijk verband tussen hypothermie en periprothetische infecties nog niet goed onderzocht. **Hoofdstuk 2** onderzocht daarom de mogelijke relatie tussen het optreden van perioperatieve hypothermie en het risico op PGI. De onderzoeksvragen van deze studie waren als volgt:

1. Is er een associatie tussen hypothermie en PGI?
2. Is de incidentie van hypothermie onderhevig aan veranderingen in de loop van de tijd?

Van januari 2011 tot december 2014 werden alle patiënten die een electieve primaire unilaterale totale knie- of heupvervanging ondergingen in de studie opgenomen. Voor, tijdens en na de operatie werd de kerntemperatuur van de patiënt gemeten. ilde hypothermie werd gedefinieerd als een kerntemperatuur tussen 35 en 36°C, terwijl ernstige hypothermie gedefinieerd werd als een kerntemperatuur onder de 35°C. Potentiële risicofactoren zoals leeftijd, BMI, geslacht, type gewrichtsvervangingen, anesthesie, operatieduur, bloedverlies en operatiedatum werden geanalyseerd.

De incidentie van PGI was 1,0% bij hypothermische patiënten versus 1,9% bij normothermische patiënten (p=0.27). Dit resulteerde in een niet-significante relatieve risicoratio van 0,52. Dit is niet in lijn met de eerdergenoemde bevindingen die een verhoogd infectierisico suggereren. Een mogelijke verklaring hiervoor is dat misschien alleen ernstige hypothermie een verhoogd periprothetisch infectierisico geeft. Hiernaast zou het kunnen zijn dat het ziekenhuispersoneel, in het geval van patiënten die een groter risico op periprothetische infecties lopen, extra aandacht heeft gehad voor hypothermiepreventie. Ook zouden andere factoren dan hypothermie invloedrijker kunnen zijn bij de ontwikkeling van periprothetische infecties. Bijvoorbeeld: een hogere BMI is geassocieerd met een hogere kerntemperatuur, maar leidt ook tot een hoger risico op PGI.

Ondanks het aanzienlijke aantal patiënten had onze studie niet genoeg “power” om een statistisch significant verschil aan te tonen. Dit heeft mogelijk te maken met de lage incidentie van PGI in de onderzoeksgroep.

Interessant is dat onze studie een afname in de mate van hypothermie over de tijd constateerde, waarbij milde hypothermie gedurende de studieperiode stabiel afnam, met een plateau na twee jaar. Ook deze afname is waarschijnlijk te wijten aan een verhoogd bewustzijn bij personeel, gecombineerd met een betere toepassing van pre-operatieve verwarmingsstrategieën. De algehele incidentie van hypothermie in primaire operaties was 11,7% in deze studie, een aanzienlijke daling ten opzichte van 26,7% in een eerdere studie ook in ons ziekenhuis is verricht.

Nasale kolonisatie van Staphylococcus aureus

In **Hoofdstuk 3** werd gekeken naar de effectiviteit van pre-operatieve nasale screening en de daaropvolgende eradicatie van Staphylococcus aureus. De Staphylococcus aureus bacterie is de belangrijkste veroorzaker van postoperatieve wondinfecties, waarbij nasale dragers van deze bacterie een hoger risico lopen om deze wondinfecties te ontwikkelen. Het eradiceren van nasale Staphylococcus aureus is effectief gebleken in het verlagen van de kans op postoperatieve wondinfecties na verschillende chirurgische procedures. Het is echter onduidelijk of deze aanpak ook zou kunnen

leiden tot een daadwerkelijke daling van periprothetische infecties (PGI’s) na een totale heupprothese (THP) of totale knieprothese (TKP). **Hoofdstuk 3** onderzocht daarom de effectiviteit van een preoperatief screening- en eradicatieprotocol voor Staphylococcus aureus in het kader van PGI’s. Deze studie had de volgende onderzoeksvragen:

1. Is screening en eliminatie van Staphylococcus aureus een effectief middel om de incidentie van vroege PGI te verlagen?
2. Vermindert screening en eradicatie van nasale Staphylococcus aureus met mupirocine de door Staphylococcus aureus veroorzaakte vroege PGI?

Alle primaire THP en TKP die tussen januari 2006 en april 2018 zijn uitgevoerd in het Rijnstate ziekenhuis in Arnhem werden retrospectief geanalyseerd met speciale aandacht voor het optreden van (vroege) PGI. Gegevens over demografie, risicofactoren voor infectie (ASA-classificatie, Body Mass Index, roken, diabetes) en type prothese werden verzameld. In oktober 2010 werd in het Rijnstate een preoperatief screening- en eradicatieprotocol geïntroduceerd, gericht op nasale Staphylococcus aureus. De incidentie van PGI’s werd vergeleken vóór (controlegroep) en na (screeningsgroep) de implementatie van dit protocol.

Statistische analyse toonde echter geen statistisch significant verschil aan in de kans op PGI’s tussen de gescreende groep (1,3%) en de controlegroep (1,7%) (OR: 0,78; 95% CI: 0,55 – 1,11; p = 0,18). De incidentie van PGI’s veroorzaakt door Staphylococcus aureus was 0,6% in de screeningsgroep versus 1,1% in de controlegroep (OR: 0,58; 95% CI: 0,36 – 0,92; p = 0,02). De incidentie van vroege PGI’s veroorzaakt door andere pathogenen dan Staphylococcus aureus was 0,9% in de screeningsgroep en 0,8% in de controlegroep (OR: 1,05; 95% CI: 0,65 – 1,71; p = 0,82).

Deze studie toont dus enige afname van PGI’s veroorzaakt door Staphylococcus aureus, zonder een statistisch significante algehele daling van de PGI-incidentie na de invoering van het screening- en eradicatieprotocol. Om deze bevinding goed te duiden, is het van belang om zowel de statistische significantie als de klinische relevantie van deze resultaten en de daarmee verbonden kosten in overweging te nemen. Het aanzienlijke aantal screeningsprocedures dat nodig is om het waargenomen significante effect te bereiken kan hierbij niet worden genegeerd. De klinische voordelen van de toepassing van screening en eradicatie van Staphylococcus aureus moeten niet worden overschat, gezien de kostbare en arbeidsintensieve aard van deze procedure.

Ook in het geval van adequate screening van dragers van Staphylococcus aureus bestaan er twijfels over de effectiviteit van deze techniek, aangezien een aanzienlijk deel van de dragers mogelijk toch nog ongeïdentificeerd blijft met deze methode. Bovendien kunnen sommige patiënten mogelijk gekoloniseerd blijven, zelfs na het ondergaan van een eradicatie behandeling. Een alternatieve benadering zou universele dekolonisatie kunnen zijn (het behandelen van alle patiënten met nasaal mupirocine zonder voorafgaande screening) als een mogelijk effectievere en kostenbesparende methode voor het verminderen van vroege periprothetische gewrichtsinfecties. Een aanzienlijk nadeel van universele dekolonisatie is echter het risico van het bevorderen van mupirocine-resistentie door de overmatige behandeling van 74% van de patiënten (waarvan 26% dragers van Staphylococcus aureus waren).

De bevindingen van deze studie bieden aanvullende ondersteuning voor het evalueren van de werkelijke klinische voordelen van de al wijdverspreide adoptie van screening en dekolonisatie van Staphylococcus aureus bij electieve totale gewrichtsvervanging. Deze studie suggereert dat, in het licht van de kostbare en arbeidsintensievere aspecten van deze protocollen, het klinische voordeel niet moet worden overschat.

Het verwijderen van osteosynthese materiaal en vervolgens plaatsen van een totale heupprothese

In **Hoofdstuk 4** werd de relevantie van het verwijderen van eerder aangebracht osteosynthesemateriaal wegens een heupfractuur onder de loep genomen. Eerdere studies suggereerden een verhoogd risico op een PGI na THP bij patiënten bij wie eerder een osteosynthese aan de desbetreffende heup was verricht. Recentere studies hebben dit echter weer tegengesproken. Derhalve blijven er tegenstrijdige opvattingen bestaan in de literatuur over het mogelijk verhoogde infectierisico dat samengaat met de plaatsing van een totale heupprothese in combinatie met de gelijktijdige verwijdering van het osteosynthesemateriaal. Er bestaat onzekerheid over de vraag of een zogenaamde eenstapsprocedure, waarbij zowel osteosynthesemateriaal wordt verwijderd als een heupprothese wordt geplaatst in een operatie, of een tweestapsprocedure, met een pauze tussen de ingrepen, veiliger is. **Hoofdstuk 4** had als doel de incidentie van PGI na THP te onderzoeken waarbij eerder aangebracht osteosynthesemateriaal moest worden verwijderd. Hierbij werden eenstaps- en tweestaps THP-procedures, met elkaar vergeleken. De onderzoeksvragen van deze studie waren als volgt:

1. Wat is de incidentie van vroege PGI na THP waarbij ook osteosynthesemateriaal is verwijderd)?

2. Wat zijn de incidenties van vroege PGI na het in één stap verwijderen van plaatmateriaal en plaatsen van een THP versus de procedure met 2 operatie stappen?

Alle patiënten die tussen januari 2006 en maart 2018 een THP hebben gekregen, waarbij ook gelijktijdig of eerder osteosynthesemateriaal is verwijderd, werden geanalyseerd om de incidentie van vroege PGI te bepalen. Bekende risicofactoren voor PGI op het moment van de operatie werden geïdentificeerd, en de incidentie van vroege PGI werd vergeleken tussen eenstaps- en tweestaps THP-procedures.

In totaal ondergingen 145 patiënten een THP implantatie met eerdere of gelijktijdige verwijdering van osteosynthesemateriaal. Hiervan is dit bij 52 patiënten als een tweestapsprocedure gedaan en bij 93 patiënten als een eenstapsprocedure. Er waren geen statistisch significante verschillen tussen de twee groepen met betrekking tot de preoperatieve hemoglobinewaarden, het tijdsinterval tussen interne fixatie en THP, het gebruik van antibiotica-verrijkt cement tijdens de arthroplastiek, de BMI en de ASA-classificatie. De algehele incidentie van PGI in deze studie was 6,9%. In de eenstapsgroep was deze incidentie 8,6%, en in de tweestapsgroep 3,8% (p=0,23).

Deze resultaten wijzen op een mogelijk verhoogd risico op PJI na THP met gelijktijdige verwijderen van osteosynthese materiaal. Het verschil tussen onze bevindingen en die van andere recente studies kan te wijten zijn aan variaties in de patiëntpopulaties, aangezien ons onderzoek is uitgevoerd in een groot algemeen onderwijsziekenhuis en niet in een tertiair orthopedisch centrum. Bovendien is het percentage patiënten met ASA-classificaties 3 en 4 in onze studie significant hoger dan in andere studies, wat het risico op PJI in deze populatie zou kunnen verhogen. De beslissing om de osteosynthese al dan niet gelijktijdig met de THP te verwijderen blijft onderwerp van discussie bij gebrek aan bewijs van hoge kwaliteit. In dit onderzoek zou de lagere incidentie van PGI na de tweestaps procedure een voordeel ten opzichte van de eenstaps methode kunnen aangeven, echter was dit verschil niet statistisch significant vanwege het beperkte aantal patiënten met een PGI.

De beslissing om osteosynthesemateriaal gelijktijdig met het implanteren van een THP te verwijderen of als een aparte procedure uit te voeren blijft een onderwerp van discussie. Er is onvoldoende hoogwaardig bewijs om een van beide benaderingen te ondersteunen. In onze studie kan de 3,8% incidentie van vroege PGI die werd waargenomen na de tweestaps procedures duiden op een klinisch voordeel ten opzichte van de eenstaps methode. Echter, dit verschil was niet statistisch significant door het beperkte aantal PGI-gevallen. Slechts twee erkende risicofactoren voor PJI verschilden significant tussen de groepen: de duur van de operatie en de leeftijd van

de patiënt, terwijl BMI en ASA-classificatie geen effect lieten zien. De operatieduur was langer voor de eenstaps groep, zoals verwacht, vanwege de noodzaak van aanvullende chirurgische handelingen. Toch moet men voorzichtig zijn bij het trekken van conclusies over dit onderwerp, aangezien de beslissing om een eenstaps- of tweestaps procedure te gebruiken niet gestandaardiseerd was. Dit introduceert de mogelijkheid van confounding door indicatie. Als gevolg hiervan bestaat er een aanzienlijke kans op selectie-bias. Deze tendens heeft geleid tot een voorkeur voor eenstaps procedures bij relatief kwetsbare patiënten die zich presenteren met ernstige en acute pijn, waarbij een tweestaps benadering minder haalbaar zou zijn.

Ongeacht of een eenstaps- of tweestapsprocedure werd uitgevoerd, werd een relatief hoge incidentie van PJI waargenomen. Men zou zich dus in ieder geval bewust moeten zijn van het verhoogde risico en een tweestapsprocedure zou in dit kader overwogen moeten worden bij patiënten die deze aanpak kunnen verdragen.

Type anesthesie

Ondanks de toenemende bewustwording van het belang van het voorkomen van PGI, blijft de invloed van sommige procedure-gerelateerde factoren, zoals het type anesthesie, onduidelijk. Recent onderzoek heeft aangetoond dat spinale anesthesie het risico op postoperatieve wondinfecties mogelijk kan verlagen vergeleken met algehele anesthesie. Opmerkelijk is dat er nog geen studies zijn uitgevoerd die de rol van anesthesie tijdens THP en TKP hebben geëvalueerd met duidelijk gedefinieerde criteria voor periprothetische infecties. **Hoofdstuk 5** onderzocht daarom de relatie tussen het type anesthesie (spinaal of algeheel) en het optreden van periprothetische infecties na THP of TKP in een grootschalig cohort. Er werd in deze studie één onderzoeksvraag geformuleerd:

1. Is er een associatie tussen het type anesthesie (d.w.z. spinaal of algeheel) en de incidentie van PGI na electieve THP of TKP?

Alle opeenvolgende patiënten die tussen januari 2014 en december 2017 electieve primaire unilaterale TKP of THP ondergingen in het Rijnstate ziekenhuis in Arnhem, Nederland, werden in de studie opgenomen. Patiënten werden uitgesloten voor deze studie als de indicatie voor de operatie een fractuur was, of als ze eerder een osteosynthese aan het aangedane gewricht hadden ondergaan.

PGI kwamen voor bij 1,7% van de patiënten in de algemene anesthesiegroep en bij 0,8% van de spinale anesthesiegroep. Het multivariabele logistische regressiemodel gaf een odds ratio van 2,0 (95% CI 1,0 - 3,7) voor periprothetische infecties na algehele anesthesie in vergelijking met patiënten die met spinale anesthesie waren behandeld.

Deze resultaten wijzen op een verhoogd risico op PGI na THP of TKP onder algehele anesthesie. Het mechanisme waardoor algehele anesthesie het risico op infectie kan verhogen, of hoe spinale anesthesie dit risico kan verlagen, blijft onduidelijk. Een mogelijke verklaring is dat spinale anesthesie de weefseloxygenatie kan verbeteren, wat mogelijk te wijten is aan de vasodilatoire effecten daarvan. Naast verbeterde weefseloxygenatie wordt neuraxiale anesthesie in het algemeen geassocieerd met minder bloedverlies en een lagere incidentie van hyperglykemie, die beiden immunosuppressieve effecten kunnen hebben.

In tegenstelling tot spinale anesthesie kunnen bepaalde anesthetica die bij algehele anesthesie worden gebruikt de chemotactische migratie van leukocyten, fagocytose en lymfocytfunctie belemmeren en zelfs bacteriegroei bevorderen in gevallen van besmetting. Daarnaast hebben studies die algehele en spinale anesthesie vergelijken, aangetoond dat de immunosuppressieve effecten die gepaard gaan met spinale anesthesie minimaal zijn.

Concluderend suggereert deze studie een mogelijke link tussen algehele anesthesie en PGI, maar verdere grootschalige studies zijn nodig om deze klinisch significante relatie verder te verhelderen.

DEEL II – DIAGNOSTIEK

Als preventie niet lukt, is een nauwkeurige diagnose van PGI essentieel. Ten eerste is een tijdige en precieze identificatie van PGI cruciaal voor het starten van passende en effectieve behandelingsstrategieën, die chirurgische ingrepen, antibioticatherapie of zelfs revisie-chirurgie kunnen omvatten. Een onjuiste of vertraagde diagnose kan leiden tot onjuiste behandelingen, waardoor de toestand van de patiënt verslechtert en het lijden wordt verlengd. Dit heeft mogelijk catastrofale gevolgen, inclusief verlies van functie van het ledemaat of een systemische infectie. Ten tweede zorgt het stellen van een nauwkeurige diagnose ervoor dat er goed onderscheid gemaakt kan worden tussen PGI en andere complicaties die na de operatie kunnen optreden, zoals aseptische loslating of ontstekingsreacties die niet gerelateerd zijn aan infectie. Een verkeerde diagnose kan leiden tot onnodige en daarmee schadelijke ingrepen. Dit veroorzaakt meer morbiditeit voor de patiënt en verhoogt de zorgkosten die gepaard gaan met langdurige ziekenhuisopnames, extra operaties en ineffectieve behandelingen.

Weefselkweken worden beschouwd als de gouden standaard voor het diagnosticeren van PGI omdat ze de aanwezigheid van bacteriën of andere pathogenen in de weefsels

rond het prothetische gewricht rechtstreeks identificeren. Dit biedt derhalve definitief bewijs van infectie. Het verkrijgen van weefselkweken vóór de definitieve operatie vereist echter een extra invasieve chirurgische procedure. Laatstgenoemde is uiteraard onwenselijk omdat dit risico's met zich meebrengt zonder dat het direct therapeutische voordelen voor de patiënt oplevert. Onder deze risico's valt ook infectie door deze nieuwe operatie maar bijvoorbeeld ook bloedingen of complicaties gerelateerd aan anesthesie. Een belangrijk nadeel van het nemen van intra-operatieve weefselkweken tijdens de revisieprocedure is de tijd die het kost totdat de kweekresultaten beschikbaar zijn. Weefselkweken hebben vaak enkele dagen nodig om te groeien, waarbij sommige bacteriën zelfs langere incubatietijden tot 2 weken vereisen. Daarom zou een betrouwbare en snelle test om PGI vóór of tijdens de operatie te identificeren, de klinische besluitvorming en daarmee de effectiviteit van de behandeling aanzienlijk verbeteren.

The Synovasure® lateral flow test for diagnosing PJI

Het zorgvuldig diagnosticeren van periprothetische infecties is momenteel niet altijd haalbaar. Er is op dit moment geen volledig betrouwbare methode om intra-operatief vast te stellen of er sprake is van een infectie, of niet. Om dit probleem aan te pakken heeft de Musculoskeletal Infection Society (MSIS) criteria vastgesteld die de besluitvorming bij de evaluatie van vermoedelijke periprothetische infecties moet verbeteren. Dit definitiesysteem is echter niet waterdicht. Helaas bestaat er ook niet één betrouwbare, gestandaardiseerde test voor het diagnosticeren van een periprothetische infectie. Een snelle en betrouwbare test die in staat is om intra-operatief onderscheid te maken tussen geïnfecteerde en niet-geïnfecteerde protheses zou daarom van onschatbare waarde zijn. Een belangrijke indicator voor het vaststellen van infectie tijdens een operatie, volgens de MSIS, is de aanwezigheid van verhoogde niveaus van α-defensine in de synoviale vloeistof van het prothetische geïnfecteerde gewricht. Om een snellere besluitvorming tussen "septische" en "aseptische" chirurgische behandelingen te faciliteren, is er een commercieel beschikbare sneltest ontwikkeld die reageert op de aanwezigheid van dit α-defensine in het synoviale vloeistof. In **Hoofdstuk 6** werd de effectiviteit van een dergelijke test, de Synovasure® test, geëvalueerd. In deze studie werden de volgende onderzoeksvragen geformuleerd:

1. Wat is de sensitiviteit van de Synovasure® test voor het diagnosticeren van PGI?
2. Zijn vals-negatieve resultaten geassocieerd met de aanwezigheid van metallose?

In een prospectieve studie werden 37 patiënten die een revisieoperatie ondergingen voor vermoedelijk vroeg aseptisch falen van de prothese (minder dan 3 jaar na primaire arthroplastiek) geïncludeerd. De Synovasure® test werd intra-operatief

gebruikt (om de aseptische aard van de implantaatloslating te bevestigen) en in alle gevallen werden ook 6 weefselkweken afgenomen.

Van de 37 geïncludeerde patiënten werd uiteindelijk bij vijf patiënten een periprothetische infectie gediagnosticeerd door bacteriële groei in de weefselkweken. Bij slechts één van deze vijf patiënten was sprake van een positieve Synovasure® test, wat een sensitiviteit van 20% opleverde. Er werden geen fout-positieve Synovasure-tests waargenomen, zelfs niet in het geval van de aanwezigheid van metallose. Metallose werd echter slechts bij één patiënt vastgesteld.

In tegenstelling tot eerdere studies richtte deze studie zich specifiek op een uniforme subgroep van patiënten die een revisieoperatie ondergingen vanwege (vermoedelijk) vroege aseptische loslating. Deze bevindingen suggereren dat de Synovasure® lateral flow test slechts beperkte extra waarde biedt voor intra-operatieve exclusie van periprothetische infecties veroorzaakt door laagvirulente micro-organismen in het geval van vermoedelijk vroeg aseptisch falen van de THP of TKP.

DEEL III – BEHANDELING

Empirische antibiotica

Débridement, antibiotica & implantaat retentie (DAIR) is de aangewezen behandeling van een acute PGI. Hierbij vindt een uitgebreid chirurgisch débridement plaats waarbij bij voorkeur de uitwisselbare delen van het implantaat vervangen worden, weefselkweken worden afgenomen en de prothese verder ongemoeid gelaten wordt. Hierna wordt direct gestart met empirische antibiotica, welke gericht zijn op de vermoedelijke pathogeen. De juiste keuze van antibioticabehandeling is uiteraard van belang voor een succesvolle behandeling. Sommige studies hebben zelfs een verband aangetoond tussen ineffectieve empirische antibiotica en het falen van de behandeling. Echter, de verkregen weefselkweken uit de operatie hebben vaak meerdere dagen nodig voordat de verantwoordelijke pathogeen wordt geïdentificeerd. Dat betekent dat er dus ook dan pas zekerheid is over het meest geschikte antibioticum. Totdat dit duidelijk is, moet de antibiotica empirisch worden toegediend. In **Hoofdstuk 7** werd gepoogd de meest voorkomende pathogenen die vroege PGI veroorzaken te identificeren samen met hun antibioticagevoeligheid. Dit alles om beter inzicht te krijgen in de optimale empirische antibioticatherapie direct na de DAIR operatie.

Alle opeenvolgende patiënten die binnen drie maanden na primaire unilaterale TKP of THP tussen januari 2011 en december 2018 DAIR ondergingen in het Rijnstate

ziekenhuis (Arnhem, Nederland), werden retrospectief geïdentificeerd aan de hand van de elektronische medische dossiers van het ziekenhuis. Informatie over de identiteit van de veroorzakende pathogenen, hun antimicrobiële gevoeligheid en het aantal postoperatieve dagen totdat culturen bacteriële groei vertoonden, werd verzameld.

In totaal werden 111 vroege PGI's geïdentificeerd, waarvan 65 (59%) monobacterieel en 46 (41%) polybacterieel waren. Van de geïsoleerde pathogenen was Staphylococcus aureus de meest voorkomende, met betrokkenheid in 53 casus. Tweeënzeventig procent van alle geïdentificeerde pathogenen was gevoelig voor vancomycine. Dit percentage kon verder verhoogd kon worden tot ongeveer 90% door een extra antibioticum gericht op gram-negatieve bacteriën toe te voegen. Bacteriële groei in de afgenomen weefselkweken werd in 98% van de gevallen tegen de vijfde postoperatieve dag gedetecteerd en alle gram-negatieve bacteriën toonden positieve weefselkweken tegen de vierde postoperatieve dag.

De identificatie van Staphylococcus aureus en coagulase-negatieve stafylokokken (CNS) als de meest voorkomende pathogenen, samen met de reeks andere geïsoleerde pathogenen in deze studie, sluit aan bij bevindingen van verschillende eerdere studies die zijn uitgevoerd. De generaliseerbaarheid van de aanbevelingen uit deze studies waar vaak ook veel MRSA bacteriën werden gediagnosticeerd naar regio's met een lagere incidentie van MRSA is echter twijfelachtig. In onze studie werden namelijk geen infecties met MRSA gedetecteerd, maar vancomycine toonde desondanks de hoogste dekking aan van alle geanalyseerde monotherapie-antibiotica. Deze dekking zou kunnen worden verbeterd door ceftriaxon of ciprofloxacine toe te voegen om de gram-negatieve pathogenen aan te pakken. Het is echter belangrijk om de aanzienlijke nadelen van vancomycine in overweging te nemen, zoals de hogere toxiciteit in vergelijking met bètalactam-antibiotica, de noodzaak om bloedspiegels te monitoren, mogelijk een verminderde effectiviteit tegen methicilline-gevoelige Staphylococcus aureus en de suboptimale activiteit tegen biofilms. Dit laatste is belangrijk, aangezien het impliceert dat een hoge dekking niet noodzakelijkerwijs een hoge effectiviteit betekent.

Op basis van deze studie kan empirische behandeling van gram-negatieve pathogenen veilig op dag 4 worden beëindigd, indien op dat moment geen groei van deze pathogenen is vastgesteld. Negenentachtig procent van alle kweekmonsters vertoonde bacteriële groei tegen de vijfde dag. Gezien deze bevinding en het feit dat 30% van de primaire DAIR-procedures vanwege de afwezigheid van PJI uit deze studie zijn uitgesloten, kunnen er omstandigheden zijn waarin het voortijdig stoppen van empirische antibiotica gerechtvaardigd is in gevallen met een lagere

waarschijnlijkheid van infectie. Uiteraard is het hierbij essentieel om de beslissing om antibiotica te staken bij patiënten die al een preoperatieve antibioticabehandeling hebben ontvangen, niet te lichtzinnig te nemen.

Herhaalde DAIR in het geval van het niet verkrijgen van vroege controle over de infectie

De succeskans van DAIR ingreep om een infectie onder controle te krijgen is soms maar 26%. Dit wijst erop dat het falen van een DAIR niet ongebruikelijk is. Wanneer een initiële DAIR-procedure mislukt, moet de chirurg beslissen of hij de DAIR-procedure herhaalt of verdergaat met een eenstaps- of tweestaps revisie van het geïnfecteerde implantaat. Hoewel een herhaalde DAIR-procedure overwogen kan worden, is deze strategie zeer controversieel. Echter, als een herhaalde DAIR-procedure uitgebreidere revisiechirurgie kan voorkomen, kan dit zeker van grote waarde zijn. In **hoofdstuk 8** werd de effectiviteit van herhaalde DAIR-procedures om een infectie alsnog onder controle te krijgen bestudeerd. De volgende onderzoeksvragen werden geformuleerd:

1. Wat is de kans van falen van een herhaalde DAIR procedure in het geval van niet verkregen vroege infectiecontrole over vroege PGI?
2. Hoe verhouden de resultaten van de bovengenoemde vraag zich tot de resultaten na een enkele DAIR procedure waarbij wel vroege infectie controle verkregen was?

Alle DAIR-procedures die van 2010 tot 2019 in het Rijnstate ziekenhuis (Arnhem, Nederland) zijn uitgevoerd voor vroege PGI na primaire THP of TKP, werden retrospectief beoordeeld. In dit onderzoek leidde het niet verkrijgen van vroege controle over de infectie (binnen een maand na DAIR) tot een herhaalde DAIR-procedure. Follow-up beoordelingen werden voor alle gevallen uitgevoerd tot 2 jaar na de operatie. Kaplan-Meier overlevingsanalyse werd gebruikt voor zowel de eenmalige als de herhaalde DAIR-groepen. Hiernaast werden Cox-regressieanalyses uitgevoerd om risicofactoren te identificeren die geassocieerd zijn met het falen van het implantaat na herhaalde DAIR.

In totaal werden 124 gevallen van vroege PGI geanalyseerd. Bij enkele DAIR-procedures werd in 69,4% (n = 86) van de gevallen adequate infectiecontrole bereikt, terwijl in 30,6% (n = 38) een herhaalde DAIR verricht werd. Na twee jaar werd in 9,9% van de gevallen van de enkele DAIR-groep en in 22,2% van de herhaalde DAIR-groep het implantaat alsnog verwijderd. Er werden geen statistisch significante associaties gevonden tussen het falen van herhaalde DAIR en de potentiële risicofactoren.

Beschikbare studies over herhaalde DAIR procedures zijn schaars, heterogeen en bevatten tegenstrijdige conclusies. Onze bevindingen suggereren echter dat een herhaalde DAIR-procedure een te overwegen behandelingsoptie kan zijn in deze specifieke context (primaire THP/TKP, vroege periprothetische infectie en het niet verkrijgen van vroege controle over de infectie na de eerste DAIR ingreep), aangezien meer dan 75% van de herhaalde DAIR-procedures in staat was om implantaatverwijdering te voorkomen.

Veel van de eerder verrichte studies analyseren verschillende indicaties voor DAIR, zoals late (hematogene) infecties en infecties na revisie van totale gewrichtsvervanging (TGV). Deze diversiteit in patiëntprofielen, procedurele benaderingen en infectietypen kan een aanzienlijke invloed hebben gehad op de behandelresultaten in deze studies. Dit kan hebben bijgedragen aan het brede scala van gerapporteerde succespercentages. In tegenstelling tot deze eerdere studies richt deze studie zich op een uniformer cohort van patiënten, waarbij we alleen kijken naar vroege PGI na primaire electieve TKP of THP. Derhalve kan wat ons betreft een herhaalde DAIR in deze specifieke context zeker overwogen worden, waarbij factoren zoals de reviseerbaarheid van het implantaat, eventuele opties voor een one-stage revisie, de co-morbiditeiten van de patiënt en de antibioticagevoeligheid van de pathogenen in overweging moeten worden genomen.

CONCLUSIES, AANBEVELINGEN EN TOEKOMSTIGE PERSPECTIEVEN

Een periprothetische gewrichtinfectie (PGI) vormen een substantiële belasting voor zowel patiënten als de samenleving vanwege de grote impact op gezondheidsuitkomsten en zorgkosten. Voor patiënten kan PGI leiden tot aanhoudende pijn, verminderde mobiliteit en een significante verslechtering van hun kwaliteit van leven, vaak met de noodzaak voor complexe behandelingen, verlengde ziekenhuisopnames en meerdere operaties. Op maatschappelijk niveau draagt de verhoogde vraag naar zorgmiddelen, waaronder langdurige revalidatie en nazorg, evenals het verlies aan productiviteit door hersteltijden, bij aan hogere algehele medische kosten en legt dit meer druk op de zorgsystemen. De veelzijdige uitdagingen die PGI met zich meebrengt, benadrukken de noodzaak voor effectieve preventie, vroege diagnostiek en adequate behandelstrategieën.

Elk onderzoek in deze thesis heeft zich gericht op ten minste een van deze aspecten van PGI, waarbij de betekenis van aanpasbare risicofactoren, innovatieve diagnostische technieken en behandelmethoden onder de aandacht is gebracht. Door deze elementen grondig te onderzoeken, willen we bijdragen aan de voortdurende

inspanningen om PJI beter te beheersen en uiteindelijk de kwaliteit van zorg voor patiënten die een gewrichtsvervangende operatie ondergaan te verbeteren. Dit heeft geleid tot de volgende conclusies en aanbevelingen voor de orthopedische praktijk:

1. Perioperatieve hypothermie lijkt niet direct gerelateerd te zijn aan een verhoogde kans op PGI, maar verder uitgebreid onderzoek is nodig om deze mogelijke correlatie definitief te beoordelen. Het blijft raadzaam om hypothermie te voorkomen vanwege de andere nadelige effecten op het herstel van patiënten.
2. Een pre-operatieve nasale screening op Staphylococcus aureus lijkt hooguit een beperkte effectiviteit te hebben in de preventie van PGI waarbij de kosteneffectiviteit twijfelachtig is.
3. Gelijktijdige verwijdering van hardware tijdens het plaatsen van een THP kan geassocieerd zijn met een verhoogd risico op PGI. Indien mogelijk, zou een tweestapsprocedure misschien veiliger kunnen zijn dan een eenstapsprocedure.
4. De incidentie van PGI lijkt hoger te zijn na THP/TKP onder algehele anesthesie vergeleken met spinale anesthesie. Daarom lijkt spinale anesthesie in deze context te verkiezen bij THP/TKP.
5. In een serie van vermoedelijke aseptische revisies had een α-defensine lateral flow-test geen aanvullende waarde om intra-operatief een laaggradige PGI toch uit te sluiten. De meerwaarde van deze commercieel beschikbare test ter intra-operatieve uitsluiting van een laaggradig infect lijkt beperkt.
6. Vancomycine in combinatie met een gramnegatief antibioticum biedt de hoogste dekking van potentiële pathogenen bij vroege PGI in afwachting van de definitieve uitslagen van de weefselkweken.
7. Herhaalde DAIR kan nog worden overwogen in het geval van falen van vroege PGI-controle binnen een maand na de initiële DAIR na primaire THP/TKP.

In dit proefschrift is geprobeerd waardevolle inzichten te verwerven met betrekking tot het voorkomen, de diagnostiek en de behandeling van PGI's. toch is het helder dat veel aspecten van PGI nog onduidelijk blijven en er ruimte is voor verbetering op het terrein van preventie, diagnostiek en behandeling. De multifactoriële aard van PGI vereist voortzettend wetenschappelijk onderzoek om de onderliggende mechanismen verder op te helderen waarmee hopelijk de klinische uitkomsten geoptimaliseerd kunnen worden.

Toekomstig onderzoek naar PGI moet prioriteit krijgen waar het de grootste impact kan hebben. Zoals bij elke ziekte is voorkomen beter dan genezen. Effectieve preventie van PGI zal de impact op patiënten en zorgsystemen verminderen en de noodzaak voor complexe diagnostiek en uitdagende behandelingen minimaliseren. Minder PGI's betekent minder revisieoperaties, minder lijden voor patiënten en lagere zorgkosten.

Om de incidentie van infecties na implantatieprocedures te verminderen, is het essentieel om de discipline van het personeel binnen de operatiekamer te verbeteren. Het Rijksinstituut voor Volksgezondheid en Milieu (RIVM) heeft dit onderwerp sinds 2010 in Nederland onder de aandacht gebracht, en het blijft cruciaal om waakzaam te blijven ten aanzien van deze modificeerbare factoren in de toekomst. De belangrijkste punten zijn als volgt:

1. Dien het meest geschikte profylactische antibioticum toe in de juiste dosering en op het juiste moment. Het toedienen van het antibioticum na de start van de operatie vermindert de effectiviteit ervan.
2. Zoals eerder vermeld, is het voorkomen van hypothermie van groot belang. Er moeten verschillende maatregelen worden genomen, en al het personeel in de chirurgische omgeving moet alert en aandachtig blijven.
3. Desinfecteer het operatiegebied grondig; er is bewijs dat het uitvoeren van tweemaal desinfectie effectiever is dan één keer. Operatieve handelingen dienen pas te beginnen nadat de huid volledig is opgedroogd na desinfectie, aangezien het droogproces een essentieel onderdeel is van de antimicrobiële werkzaamheid van jodium of chloorhexidine.
4. Beperk het aantal medewerkers in de operatiekamer tot het noodzakelijke minimum en voorkom onnodige bewegingen door de operatiekamerdeuren tijdens de operatie om mogelijke besmetting tijdens de operatie te beperken.

Hoewel deze richtlijnen eenvoudig lijken, blijkt het een uitdaging om consistent aan deze richtlijnen te voldoen. Een voortdurende focus op deze gedragsmaatregelen is essentieel voor het verbeteren van de patiënten uitkomsten in de toekomst.

Er zijn verschillende modificeerbare risicofactoren geïdentificeerd die een verhoogd risico op PGI lijken te geven. Er is echter nog veel controverse over de optimale strategie om deze risicofactoren te reduceren met als doel de kans op PGI te minimaliseren. Dit kan onder andere door de operatie uit te stellen voor patiënten die een verhoogd risico lopen totdat de patiënt geoptimaliseerd is en zo fit mogelijk is voor de operatie. Dit is echter niet eenvoudig. Bijvoorbeeld obesitas is geassocieerd met een hoger risico op PGI, maar er zijn veel controverses over de rol en het management van obesitas in de context van THP of TKP. Begeleiding om gewichtsverlies te bereiken slaagt er nogal eens niet in om voldoende resultaat te boeken. Een andere optie is bariatrische chirurgie. Dit is onderzocht als een methode om postoperatieve complicaties te verminderen maar blijft qua effectiviteit omstreden vanwege inconsistent bewijs van een verminderd PGI risico. Een van de problemen bij bariatrische chirurgie is dat het vaak leidt tot veranderingen in eetgewoonten, wat kan resulteren in tekorten aan essentiële voedingsstoffen, zoals eiwitten, vitamines (zoals A, C en E) en

mineralen (zoals zink). Deze voedingsstoffen zijn cruciaal voor het genezingsproces en kunnen de wondgenezing verstoren, wat uiterst ongewenst is na THP of TKP. Dit kan leiden tot een reeks negatieve uitkomsten, waaronder meer postoperatieve pijn, langere hersteltijden en helaas ook weer PGI. Deze tekorten kunnen tot wel 2 jaar na bariatrische chirurgie aanhouden. Sommige onderzoekers geven zelfs aan dat eerdere bariatrische chirurgie de kans op perioperatieve bloedtransfusies zelfs kan verhogen, evenals het risico op revisies en infecties bij langdurige follow-up. Misschien is de dikte van subcutaan vet op de locatie van de incisie wel een nauwkeurigere voorspeller van het complicatierisico dan de BMI alleen. Dit alles in ogenschouw nemende kan een goede beoordeling van de voedingsstatus van een patiënt en het corrigeren van voedingsdeficiënties wellicht wel belangrijker zijn dan het alleen het reduceren van gewicht.

De moeilijkheid betreffende hoe de aanpasbare, patiënt gerelateerde risicofactoren te optimaliseren, geldt niet alleen voor obesitas. Andere bekende risicofactoren verhogen ook het risico op PGI (bijv. diabetes mellitus, ondervoeding), maar er is veel controverse over hoe deze factoren aan te pakken. Onderzoek gericht op het verhelderen van effectieve managementstrategieën of de mechanismen waardoor ze bijdragen aan het verhoogde risico op PGI zou een grote bijdrage leveren aan de preventie van PGI.

Verder onderzoek naar het optimaliseren van de voedingsstatus (in het algemeen) kan mogelijk de incidentie van PGI na THP/TKP verminderen omdat goede voeding een cruciale rol speelt in het ondersteunen van het immuunsysteem en het bevorderen van de wondgenezing. Voedingsdeficiënties kunnen het vermogen van het lichaam om infecties te bestrijden en te herstellen van een operatie belemmeren, waardoor het risico op complicaties zoals PGI toeneemt. Door effectieve strategieën voor de voedingsoptimalisatie vóór de operatie te identificeren, kunnen zorgverleners de weerstand van patiënten tegen infecties mogelijk verbeteren, wat zou kunnen leiden tot betere resultaten en lagere percentages PGI. Dergelijk onderzoek zou dus uiteindelijk kunnen bijdragen aan veiligere chirurgische procedures.

De eerder genoemde opties om patiënten voor te bereiden op chirurgie worden in Nederland in verschillende ziekenhuizen geïmplementeerd via een stichting genaamd Fit4Surgery. Fit4Surgery is een initiatief in Nederland dat gericht is op het optimaliseren van de fysieke en mentale voorbereiding van patiënten op chirurgische ingrepen. Het programma richt zich op preoperatieve patiënten educatie en verbetering van de levensstijl, met de nadruk op het belang van lichamelijke fitness, voedingsverbetering en psychisch welzijn voorafgaand aan de operatie. Door deze modificeerbare factoren aan te pakken, streeft Fit4Surgery

ernaar om de chirurgische resultaten te verbeteren en het risico op postoperatieve complicaties te verlagen.

De primaire doelstellingen van Fit4Surgery omvatten de bevordering van de zelfbeschikking van patiënten door middel van gepersonaliseerde trainingsprogramma's, voedingsadviezen en psychologische ondersteuning. Via deze interventies pleit het initiatief voor de adoptie van gezondere gedragingen die kunnen leiden tot verbeterde hersteltijden en een betere algehele gezondheidstoestand. Door dergelijke uitgebreide preoperatieve voorbereidingen te implementeren, streeft Fit4Surgery ernaar bij te dragen aan de effectiviteit van chirurgische ingrepen en de kwaliteit van zorg die aan patiënten in het gezondheidszorgsysteem wordt geboden, te verbeteren. Ik geloof dat programma's zoals Fit4Surgery nuttig kunnen zijn bij het verminderen van complicaties zoals PGI.

Naast het optimaliseren van de patiënt, is er ook de mogelijkheid om het implantaat te optimaliseren. Recente ontwikkelingen in implantaatcoatings die zijn ontworpen om PGI te verminderen hebben zich voornamelijk gericht op het verbeteren van de antimicrobiële eigenschappen terwijl de biocompatibiliteit wordt gewaarborgd. Dit omvat de ontwikkeling van antimicrobiële coatings met metalen zoals zilver, koper of zink, die bacteriële kolonisatie remmen. Daarnaast maken antibiotica-afgevende coatings de gerichte toediening van hoge concentraties antibiotica rechtstreeks op de implantaatlocatie mogelijk, hierdoor wordt systemische blootstelling geminimaliseerd en het risico op infecties wordt verminderd. Bovendien kunnen polymeercoatings, zoals antimicrobiële polymeren of hydrogels, worden aangebracht om de hechting van bacteriën aan het implantaat te remmen. Het implementeren van deze strategieën zou nieuwe kansen kunnen bieden om de incidentie van PGI te verminderen door bacteriële kolonisatie en biofilmontwikkeling op implantaatoppervlakken te verminderen of zelfs te voorkomen.

De vraag is of het ooit mogelijk zal zijn om PGI volledig te voorkomen. Dit zou een onrealistische verwachting kunnen zijn, wat betekent dat er altijd een noodzaak zal zijn voor effectieve behandelingen van PGI. Een grote uitdaging ligt in het onderscheiden van laaggradige infecties en aseptisch implantaat falen, aangezien beide aandoeningen een andere behandelingsstrategie vereisen. Helaas zijn er momenteel geen snelle, minimaal invasieve of niet-invasieve tests beschikbaar om betrouwbaar laaggradige infecties te bevestigen of uit te sluiten. Toekomstig onderzoek dat gericht is op potentiële serum- of synoviale vloeistof gebaseerde biomarkers om aseptisch van laaggradig septisch implantaatfalen betrouwbaar te onderscheiden, zou de belasting voor patiënten aanzienlijk kunnen verminderen. Dit zou het mogelijk maken om patiënten dienovereenkomstig te behandelen, waardoor de gevolgen van onjuiste behandelingen worden geminimaliseerd.

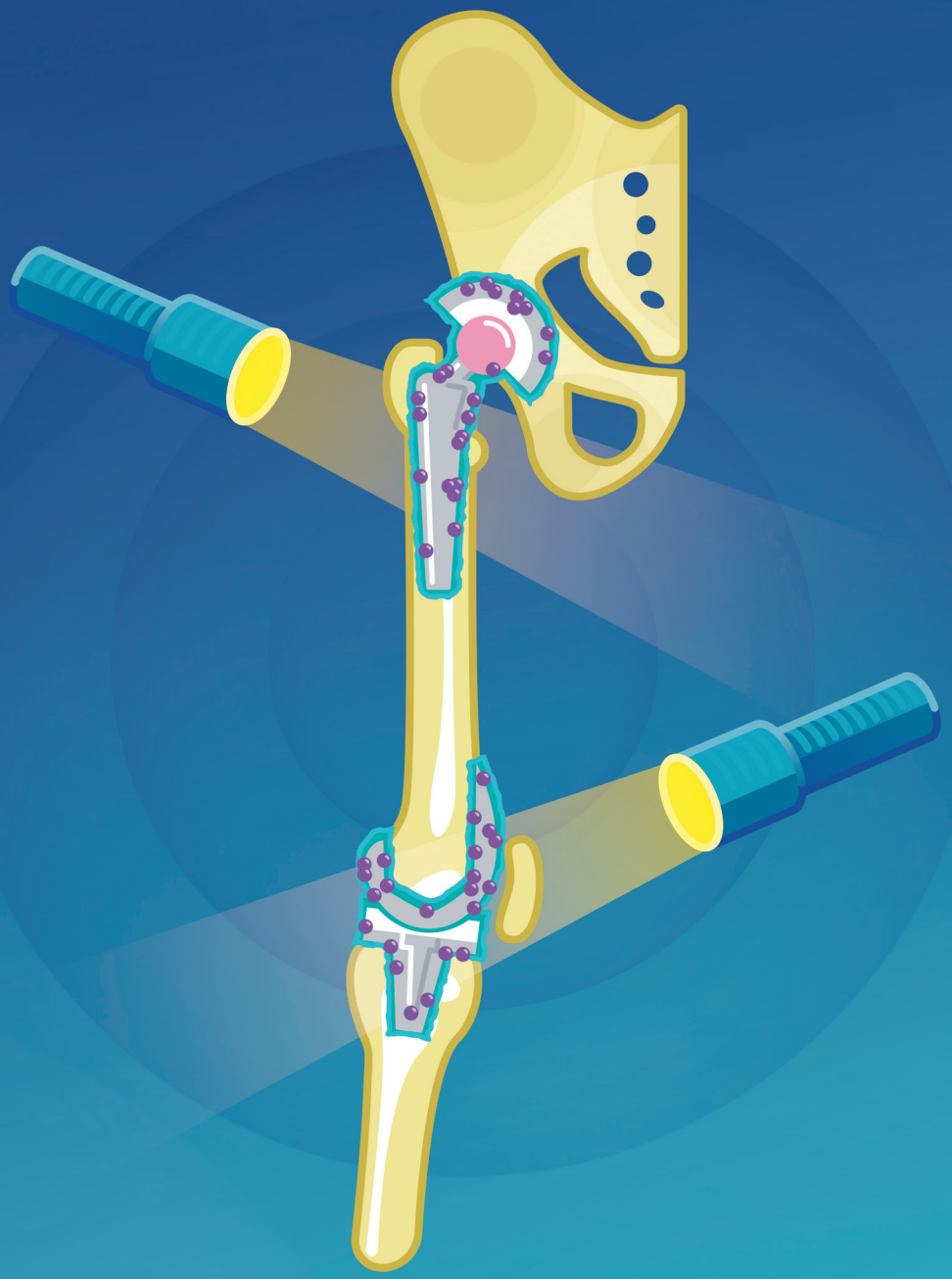
Een toekomstig perspectief op het verbeteren van de behandeling van PGI kan de implementatie van bacteriofagen zijn. Bacteriofaagtherapie heeft de mogelijkheid om bijvoorbeeld specifiek antibioticum-resistente bacteriën aan te pakken en te lyseren die PGI veroorzaken. Fagen kunnen effectief biofilms op implantaatoppervlakken doordringen en verstoren, die berucht zijn om hun resistentie tegen de traditionele antibioticabehandelingen. Bovendien kan deze therapie de afhankelijkheid van antibiotica verminderen, waardoor de risico's verbonden aan antibioticaresistentie en bijwerkingen worden geminimaliseerd. Hoewel initiële studies positieve resultaten hebben gerapporteerd, is verder klinisch onderzoek nodig om gestandaardiseerde protocollen vast te stellen en de effectiviteit en veiligheid van bacteriofaagbehandeling bij de behandeling van PGI te bevestigen.

Toekomstig onderzoek zal mogelijkerwijs factoren kunnen identificeren die zowel de preventie, diagnostiek als de behandeling van PGI kunnen verbeteren, maar waarschijnlijk zijn er ook andere manieren om de zorg voor patiënten met PGI te verbeteren. Dit kan inhouden dat de behandeling van complexe gevallen bijvoorbeeld wordt gecentraliseerd in gespecialiseerde centra. Zoals in deze thesis regelmatig is vermeld, is de incidentie van PGI laag. Dit betekent dat orthopedisch chirurgen deze kwestie niet frequent tegenkomen, laat staan therapieresistente gevallen of chronische PGI. Onderzoek suggereert dat betere behandelresultaten kunnen worden behaald wanneer de zorg wordt verleend door ervaren behandelcentra. Wellicht kunnen dus de uitkomsten worden verbeterd als uitdagende gevallen in dergelijke gespecialiseerde faciliteiten worden behandeld, bijvoorbeeld in gevallen waarin de vroege infectiecontrole na de initiële DAIR niet is bereikt. Een andere optie kan zijn om toegewijde teams op te richten binnen elk ziekenhuis dat PGI's behandeld, zodat zij aanvullende training kunnen krijgen die specifiek gericht is op PGI.

Door een fundament te leggen voor toekomstig onderzoek, beoogt dit werk verdere studies te inspireren die ons begrip van PGI's verder kunnen vergroten, wat uiteindelijk kan leiden tot verbeterde zorg. Om onze visie op PGI verder te blijven verfijnen, is het essentieel dat de orthopedische gemeenschap zich blijft inzetten voor voortdurende onderzoeksinspanningen om de impact van deze bedreiging voor patiënten en zorgsystemen te verlichten.

REFERENTIES

Zie referenties hoofdstuk 9.



APPENDICES

RESEARCH DATA MANAGEMENT

Ethics and privacy

This thesis is based on the results of research involving human participants, which were conducted in accordance with relevant national and international legislation and regulations, guidelines, codes of conduct and Radboudumc policy. This thesis is based on the results of the studies that didn't fall within the remit of the Medical Research Involving Human Subjects Act (WMO), and was in accordance with the Declaration of Helsinki. This thesis utilizes data from electronic patient records at the Rijnstate Hospital in Arnhem. The institutional ethical review board at Rijnstate Arnhem approved the use of these medical records for the studies presented in this thesis. Chapter 2 details a retrospective study conducted at the Canisius Wilhelmina Hospital (CWZ), which was also approved by the CWZ Local Ethical Committee.

Data collection and storage

The primary and secondary data acquired during this PhD were securely stored in digital format on the local server of Rijnstate Hospital's orthopedic department (on G: schijf). The data used in Chapter 2 is stored in digital format on the local server of the CWZ orthopedic department (on M: schijf). To ensure patient privacy, all data were pseudonymized, and personal information was removed. Participants' privacy was further protected through the use of encrypted and unique individual subject codes that corresponded with codes on patient and physician files.

Subject data, as obtained from the electronic patient file systems of the Rijnstate and CWZ, were entered into SPSS (SPSS Inc., Chicago, Illinois, USA) datasets. SPSS was used to perform the statistical analyses in Chapters 2, 4, 6 and 7. In Chapters 3, 5 and 8 statistical analyses were performed using R (R Foundation for Statistical Computing, Vienna, Austria).

Availability of data

Chapters 2, 5 and 6 are published open access. The data concerning this thesis will be archived for 15 years after termination of the corresponding study (i.e., publication of the analysis that used the data). Access to the database is restricted to the project members working at Rijnstate or CWZ. The datasets generated and analyzed can be obtained by contacting the corresponding authors.

PHD PORTFOLIO OF RUBEN SCHOLTEN

Department: **Orthopedics**
PhD period: **01/04/2018 – 20/10/2025**
PhD Supervisor(s): **Prof. dr. B.W. Schreurs**
PhD Co-supervisor(s): **Dr. J.L.C. van Susante & Dr. G.J. Hannink**

Training activities	**Hours**
Courses	
- GCP Course (2017)	17.00
- ATLS Provider (2019)	50.00
- CASH 1 (2019)	40.00
- PACONU (2020)	30.00
- Radboudumc - Introduction day (2021)	6.00
- RIHS - Introduction course for PhD candidates (2021)	15.00
- Stralingshygiëne voor Medisch Specialisten en aios (2021)	30.00
- Basiscursus Arthroscopie Knie (2022)	10.00
- Basiscursus Arthroscopie Schouder (2022)	10.00
- Heupprothesiologie cursus (2022)	10.00
- AO Basic Principles of Fracture Management (2022)	60.00
- Radboudumc - Scientific integrity (2024)	20.00
- Arthrex AIOS Knee Course (2024)	24.00
- ATLS Refresher (2024)	40.00
- AO Advanced Principles of Fracture Management (2024)	40.00
- Knieprothesiologie cursus (2024)	10.00
- J&J Advanced Anterior Hip Course (2025)	10.00
Seminars	
- Research meetings orthopedic department “Spiegeluur” (2021)	15.00
- Seminars and lectures (Rijnstate, Sint Maartenskliniek, RadboudUMC, approx. 100) (2025)	100.00
Conferences	
- European Bone & Joint Infection Society Congress (2016), poster presentation	30.00
- European Hip Society (2018), oral presentation	30.00
- NOV Jaarcongres (2020), oral presentation	20.00
- “Artikel van het Jaar” symposium Rijnstate (2022), oral presentation	10.00
Teaching activities	
Lecturing	
- Journal clubs & clinical presentations (2025)	50.00
Supervision of internships / other	
- Supervision of bachelor research student (2019)	28.00
Total	**705.00**

DANKWOORD

Dit proefschrift markeert het einde van een lange reis die voortkomt uit mijn interesse in de orthopedie. Het is echter een reis geweest die ik nooit alleen had kunnen volbrengen. Gedurende dit traject ben ik gezegend geweest met de acceptatie, steun, begeleiding en inspiratie van vele bijzondere mensen, waarschijnlijk te veel op te noemen, zowel professioneel als persoonlijk. Hun waardevolle bijdragen hebben niet alleen mijn onderzoek verrijkt, maar ook mijn persoonlijke en professionele groei bevorderd én een verdere carrière binnen de orthopedie mogelijk gemaakt. Met dit dankwoord wil ik mijn oprechte erkentelijkheid uitspreken voor hun bijdragen aan mij, in het tot stand komen (en uitstellen van) van dit werk.

Het begon allemaal als co-assistent in het CWZ. Mijn enthousiasme voor de orthopedie werd direct door **Sander Koëter** extra aangewakkerd. Ik werd met open armen ontvangen en ik kreeg tips, zetjes in de juiste richting en kansen om mee te werken aan wetenschappelijk onderzoek. Dit markeerde het begin van een langere, leuke samenwerking middels een wetenschappelijke stage in het CWZ in samenwerking met **Keetie Kremers** wat uiteindelijk tot 3 publicaties heeft geleid. Dit is heeft de basis gelegd van mijn wetenschappelijke carrière en dit proefschrift. Sander & Keetie, enorm bedankt voor jullie hulp, advies en begeleiding! Jullie zijn van onschatbare waarde geweest voor mij om dit pad uiteindelijk te bewandelen.

Voordat ik uiteindelijk in Rijnstate terecht kwam als ANIOS heb ik na het behalen van mijn artsendiploma eerst een jaar in het Elkerliek ziekenhuis in Helmond gewerkt. Door de zeer prettige samenwerking daar met alle orthopeden (**Harm Boons, Hub Noten, Peter Eggen, Herman Lacroix, Bryan Blaauw, Lucas Kleijn, Jan Oyen én M&M**) werd ik extra bevestigd om dit carrièrepad te vervolgen. In die periode heb ik ook onder begeleiding van Harm Boons mijn eerste artikel als eerste auteur gepubliceerd. Allemaal enorm bedankt voor jullie adviezen & geboden kansen!

Na mijn tijd in het Elkerliek ben ik weer teruggekeerd in Rijnstate. Ik moet alle orthopeden en chirurgen aldaar hartelijk danken voor hun ondersteuning, hulp en zeer prettige samenwerking. **Corné van Loon** moet ik echter specifiek bedanken. Tijdens mijn co-schappen heb ik ooit een orthopedische encyclopedie van je gekregen, waarvoor ik je moest beloven dat ik orthopeed zou worden. Deze encyclopedie heb ik nog regelmatig opengeslagen als naslagwerk tijdens het schrijven van dit proefschrift. Dank, niet alleen voor het boek maar zeker ook voor je vertrouwen en goede raad!

Job van Susante is natuurlijk essentieel geweest voor dit proefschrift als copromotor. Zijn kritische en pragmatische blik zijn de drijvende kracht geweest achter de kwaliteit van mijn proefschrift. Daarnaast is hij voor mij van onschatbare waarde geweest in het realiseren van een opleidingsplek en heb je mij de kans geboden om mijn onderzoekjes uit te breiden tot een volledig PhD traject door mij een positie als arts-onderzoeker in het Rijnstate te bieden. Daarnaast ben je ook als opleider voor mij enorm waardevol geweest, niet alleen in goede maar juist ook in slechte tijden. Ik kan jou hier niet genoeg voor bedanken.

Als naadloze aanvulling op het eerder genoemde pragmatisme was er in het Rijnstate gelukkig ook nog **Matthijs Somford**. Mede dankzij zijn laagdrempeligheid, enthousiasme en out-of-the-box ideeën werd mijn onderzoekstijd nog plezieriger dan het al was. Jouw rol als motivator en meedenker is niet te onderschatten. Heel veel dank voor alles!

Dan wil ik mijn oprechte dank uitspreken aan mijn andere copromotor, **Gerjon Hannink**. Zijn enthousiasme, nauwe betrokkenheid gedurende het gehele traject (zowel inhoudelijk als mentaal), uitgebreide kennis van de benodigde statistiek en constante beschikbaarheid zijn van onschatbare waarde geweest. Nooit te beroerd en altijd klaar om te adviseren en te begeleiden. Gerjon, jouw expertise heeft "significant" bijgedragen aan de kwaliteit en diepgang van mijn proefschrift en ik ben zeer, zeer dankbaar voor de prettige en constructieve samenwerking.

En dan wil ik uiteraard mijn speciale dank uitspreken aan mijn promotor, professor **Wim Schreurs**. Zijn enthousiasme en kritische blik, maar ook vooral zijn positiviteit hebben dit traject zeer aangenaam en stimulerend gemaakt. Zijn waardevolle feedback en laagdrempelige betrokkenheid hebben een grote rol gespeeld in het voltooien van dit proefschrift. Ik ben zeer erkentelijk voor zijn rol als supervisor gedurende deze periode.

Dit proefschrift is mede tot stand gekomen door de geboden kansen en het vertrouwen van de opleiders orthopedie in onze opleidingsregio. Derhalve wil graag ook mijn oprechte dank uitspreken aan mijn (andere) opleiders van ROGO Oost, die een essentiële rol hebben gespeeld in mijn opleiding tot orthopeed. **Wim Rijnen, Sebastiaan v.d. Groes, Marc Wagener, Arno ten Ham en Vincent Busch**: jullie expertise, begeleiding en inspirerende mentorschap hebben mijn ontwikkeling als arts en wetenschapper enorm gestimuleerd.

Ook wil ik specifiek mijn andere "opleiders" **Bart Bosker, Oscar Dorrestijn, Dennis Kok, Stijn van Gennip, Peer Konings, Bart Kuipers en Simon van Laarhoven** – nog specifiek noemen. Een koppeling met jullie betekende altijd een intensieve en waardevolle samenwerking, waarbij ik iedere keer weer veel van jullie heb geleerd maar ook plezier heb gehad. Jullie hebben niet alleen een grote bijdrage geleverd aan mijn professionele ontwikkeling, maar daarmee ook aan dit werk dat ik hier presenteer.

Graag wil ik alle **mede-auteurs** van harte bedanken voor hun waardevolle bijdragen aan dit proefschrift. Ik zal niet ieder individu benoemen, maar al jullie deskundige inzichten, kritische feedback en voortdurende steun hebben een onmisbare rol gespeeld in het tot stand komen van dit werk.

Het combineren van een PhD met de opleiding orthopedie is mij zeker vaak ook zwaar gevallen. Gelukkig wordt het leed verzacht door alle leuke collega **AIOS** met wie ik deze bijzondere periode heb mogen delen. Allen hebben een belangrijke bijdrage geleverd aan deze bijzondere tijd. Hiervan wil ik wel nog even **Philip Scheurer, Frans Bovendeert, Joris Bongers, Peter Schmitz, Thomas Eggen, Ena Colo en Maarten Mosch** even uitlichten voor hun unieke bijdrage aan de balans tussen droge materie en vloeibare inspiratie – soms gevonden in een glas, altijd in goed gezelschap.

Naast geweldige collega's heb ik gelukkig ook geweldige vrienden. **Rutger Fabritius, Dennis Arns** en **Tijs van der Meer**, sinds onze middelbare schooltijd al maatjes en echte vrienden geworden tijdens een (grotendeels) gedeelde studententijd. Ieder deed iets anders, maar wij bleven elkaar opzoeken. Van wilde jongens tot nu trotse vaders; een proces dat ik met bewondering heb gevolgd. Jullie gezelschap is altijd enorm gewaardeerd geweest en zal dat ook blijven, ongeacht hoe de tijden onvermijdelijk veranderen.

Verder kunnen de voetbalmannen van FC Kunde natuurlijk niet ontbreken. Prachtige jaren met ups en downs. Zelfs als ik weer eens geblesseerd was, was het gezelschap altijd genieten. Onze band beperkt zich allang niet meer tot alleen voetbal, en dat is prachtig. **Jasper Martin, Jules Houben, Jeroen Ijff, Jordi Kipping, Victor Schleedoorn, Maurits van Ravesteyn, Bryan Willems en Stijn Hamers**, bedankt voor jullie!

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Hoewel dit hele proefschrift schrijven een uitdaging was, is het schrijven van deze alinea zonder twijfel het allermoeilijkst. Niet omdat ik niet weet hoe ik dit moet formuleren, maar juist omdat ik weet dat mijn vader het nooit meer zal lezen. Ik zal altijd de mooie herinneringen koesteren. Helaas zijn de laatste jaren anders geweest. **Theo**, ik vind het zo ontzettend jammer dat je niet meer mee mag maken dat ik dit heb bereikt, maar ik weet dat je trots zou zijn (of het misschien ergens wel bent).

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ABOUT THE AUTHOR

Ruben Scholten was born on August 7, 1990, in the city of Nijmegen, Netherlands. He grew up in Lindenholt, a suburban area of Nijmegen.

He attended the Stedelijk Gymnasium Nijmegen for his secondary education. After completing high school, he decided to delve deeper into the biological sciences and pursued a Bachelor's degree in Biology, which he obtained in 2010. This foundation was crucial as he transitioned to a pre-master's program in medicine, further igniting his enthusiasm for the medical field.

Ruben continued his studies by enrolling in the master's program in medicine. During his clinical rotations, particularly in surgery at Canisius Wilhelmina Hospital (CWZ), he first encountered the intriguing realm of orthopedics. It was during this time that he realized his genuine interest in this specialty, compelling him to focus his future career in this direction.

To refine his research skills and expand his knowledge, Ruben undertook a scientific internship under the guidance of Sander Koëter in the CWZ. This opportunity proved to be instrumental in his development as a physician and researcher, culminating in two scientific publications.

In December 2015, after years of dedicated study, Ruben proudly earned his medical degree. He began his professional career in 2016 as an ANIOS in orthopedics at Elkerliek Hospital in Helmond. This role provided him with invaluable hands-on experience in patient care and confirmed his passion for orthopedics.

In 2017, he transitioned to a similar position as ANIOS in orthopedics at Rijnstate Hospital, which allowed him to further develop his skills and deepen his understanding of orthopedic practices. In 2018, he was accepted into the orthopedic residency program, marking a significant milestone in his career.

From 2018 to July 2019, Ruben worked as a research physician under the supervision of Job van Susante at Rijnstate Hospital. This position enabled him to combine clinical work with research aimed at periprosthetic joint infections, which ultimately led to this dissertation.

In July 2019, Ruben started as a resident at the department of surgery as part of the orthopaedic surgery training in the CWZ under the supervision of dr. Polat. In 2021 he continued residency in the Radboudumc under the supervision of dr. Rijnen and dr. ir. van de Groes. Currently, Ruben is in his final year of his orthopedic training at the Sint Maartenskliniek and Rijnstate Hospitals under the supervision of dr. Busch and drs. ten Ham, and dr. van Susante and dr. Wagener, respectively. Ruben currently lives with his partner Mieke Pijnenburg in Lent, Nijmegen.


Rijnstate


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