Strategies in prevention and treatment of prosthetic joint infections

Ewout S. Veltman

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Strategies in Prevention and Treatment of Prosthetic Joint Infections

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"Voor Deli, voor haar voorwaardelijke steun.
En voor mij, zonder wie dit boek er niet zou zijn geweest."
(vrij naar: Adam Kay, This is going to hurt, 2017)

PUBLICATIONS CONTRIBUTING TO THIS THESIS

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Similar risk of complete revision for infection with single-dose versus multiple-dose antibiotic prophylaxis in primary arthroplasty of the hip and knee: results of an observational cohort study in the Dutch Arthroplasty Register in 242,179 patients.
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Similar rate of infection eradication for functional articulating, prefabricated and custom-made spacers in 2-stage revision of the infected total hip: a literature review.
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Revision for culture-negative total knee arthroplasties, a case-control clinical evaluation of functional and patient reported outcome of two-stage revision versus one-stage revision.
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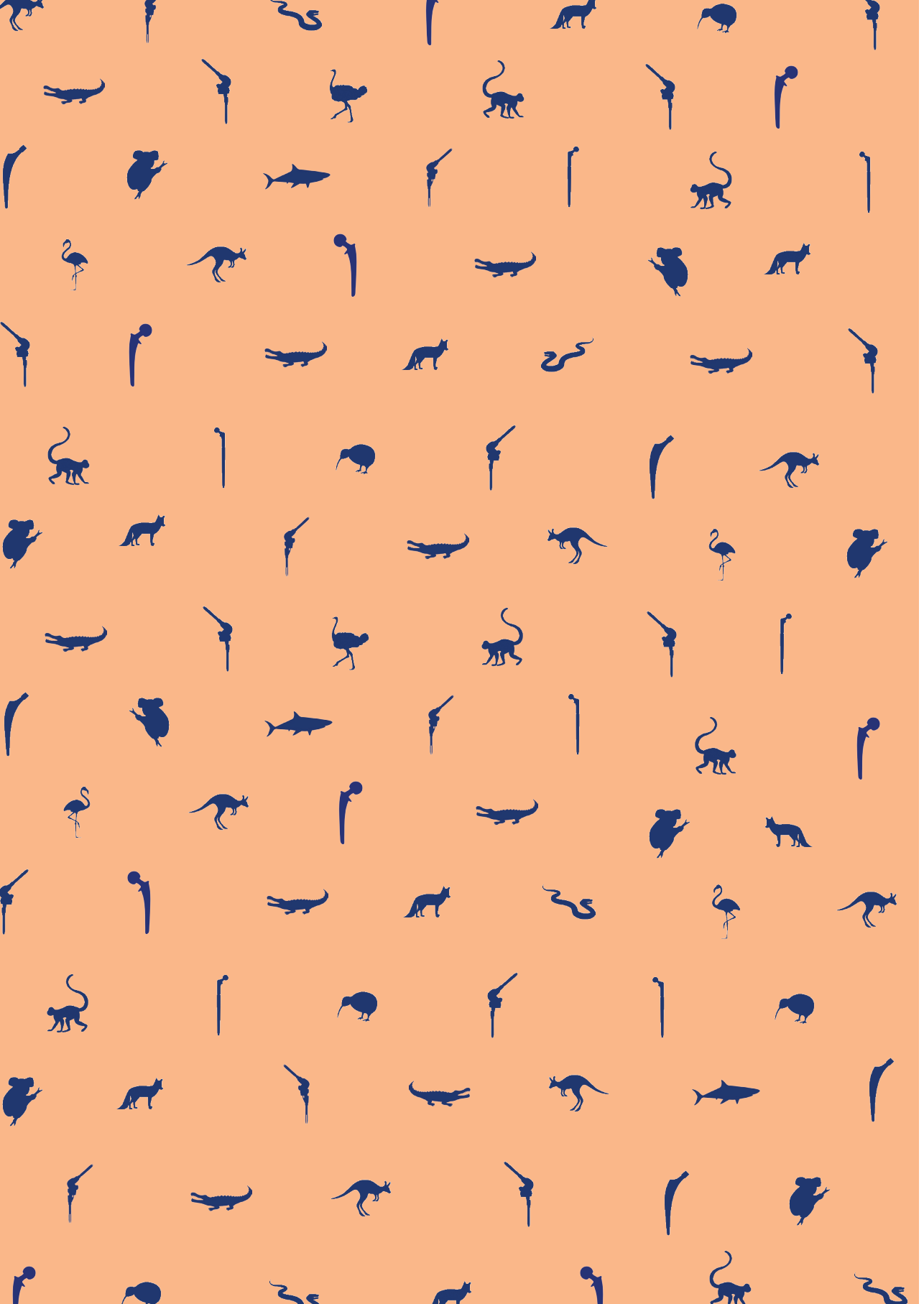

CHAPTER

1

Introduction

BACKGROUND AND PROBLEM STATEMENT

Hip and Knee Arthroplasty

Periprosthetic joint infection (PJI), along with periprosthetic fracture, is widely recognized as the most devastating complication following total hip or knee arthroplasty.[1-3] In western countries the incidence of prosthetic joint infection after primary hip or knee arthroplasty is about 2%.[4-6] For revision surgery the infection rate rapidly increases to even up to 10%.[7, 8] In the Netherlands, nearly 70 000 hip and knee arthroplasties are annually performed, while in the United States over a million patients receive a hip or knee arthroplasty every year.[9, 10] As the absolute number of primary and revision arthroplasties are expected to increase in the next decades, the absolute number of infectious complications will increase as well, even if the incidence of infection will decrease.[10, 11]

Therefore a challenge is at hand for orthopaedic surgeons worldwide, to study and optimize infection prevention and diagnosis and to determine the optimal treatment algorithms for patients with both an acute and a chronic prosthetic joint infection.

Prevention of Infection

Many risk factors for infection after primary arthroplasty are patient related.[12, 13] Relevant comorbidities include obesity, diabetes, conditions such as rheumatoid arthritis requiring immunosuppressive agents, and cardiac comorbidities requiring anticoagulation.[12, 14] Literature shows that infection risks are significantly elevated in obese patients.[14] Whether weight reduction in obese patients results in lowering the risk of infection to a normal level has yet to be determined.[12] Some of the patient behavioral risk factors for infection are also poor personal hygiene, and alcohol and smoking habits. Cessation of smoking more than four weeks preoperative reduces the percentage of wound complications and infections.[15, 16] Several preventive strategies have been used to decrease the incidence of infection, which are patient and technical measures about the perioperative period.[12, 17] Currently worldwide almost all orthopaedic departments performing arthroplasty surgery use strict perioperative treatment protocols in order to operate patients in the highest possible ultra-clean operating theatres under sterile conditions. These regimens start preoperatively by advising patients to use antibacterial soap and nose ointment to reduce colonies of *Staphylococcus aureus* bacteria at the skin.[18] Orthopaedic surgeons can decide to cancel surgery in case the patient has any wounds in the surgical field. The latter may act as an entry point for bacteria perioperatively. Finally, preoperatively, prophylactic antibiotics are administered.[19]

Intraoperatively, face masks are used to cover the nose and mouth of personnel in the operating theatre.[20] The skin is meticulously decontaminated with iodine or chlorhexidine and sterile draping is applied.[17] The surgeons wear sterile clothing and gloves, and regularly change gloves at different stages of surgery.[17, 21] All instruments used during surgery are sterilized.[17] The number of particles in air in the operating theatre has to stay below a limit of 10 colony-forming units per meter cubed (cfu/m^3) of bacteria and is controlled by a light overpressure in the OR and the use of a unidirectional laminar airflow system. Furthermore air-turbulence is reduced by limiting the number of operating theatre door movements to the minimum as well as the number of persons within the OR to a minimum.[22-24] Postoperatively a wound dressing is applied under sterile conditions.[25] However, only few of these measures have been scientifically proven to actually be effective in the prevention of PJI.[12, 26] Next to the discovery of antisepsis in the 19th century by, among others, Lister and Pasteur, antibiotic prophylaxis may be the single most effective preventive action limiting the number of prosthetic joint infections.[19, 26, 27] However, even though the importance of antibiotic prophylaxis is supported by orthopaedic and infectious disease specialists worldwide, little evidence is available about the type and duration of antibiotic prophylaxis around primary arthroplasty of the hip and knee.[28] Several studies have shown that prolonging antibiotic prophylaxis after 24 hours after surgery does not lead to a lower infection rate.[26, 29-31] Which duration of antibiotic prophylaxis is best, remains to be determined.[28] Concerning the type of antibiotic that should be used as prophylaxis more consensus exists.[28, 32] A second generation cephalosporin is recommended in countries that have a low incidence of multi-resistant Staphylococcus aureus infections, such as the countries in northern Europe including the Netherlands.[28, 33] Despite the importance of antibiotic stewardship an UK study showed no reasons why surgeons did not adhere to the national guideline on antibiotic prophylaxis in the UK.[34]

Diagnosis of Infection

Prosthetic joint infection is a complex problem. As it knows many different appearances, infection can truly be a diagnostic challenge.[35] To definitely diagnose an infection can be troublesome in many cases as it is multifactorial.[35, 36] Physicians have an increasing number of diagnostic tools available to assist them. The MusculoSkeletal Infection Society (MSIS) and the European Bone and Joint Infection Society (EBJIS) have joined forces in an attempt to find the evidence and achieve consensus during an international consensus meeting in Philadelphia in 2014 and 2018.[28, 32] To start, the medical history on former surgery and start of symptoms as well as physical examination of the patient are still important. The patient may mention

prolonged wound leakage following primary surgery, persisting wound effusion, pain when bearing weight, presence of cold chills or fever, or swelling of the joint. During physical examination special attention should be payed to the presence of hydrops, joint effusion through the scar or the presence of a fistula, or a difference in temperature of the joint and the surrounding tissue, as well as the range of motion of the joint. In addition to information collected during anamnesis and physical examination, a range of laboratory tests are available. Basic parameters such as the C-reactive protein (CRP) level, the leukocyte count or the erythrocyte sedimentation rate (ESR) can point towards infection when elevated, but may sometimes be false negative. Differences in the composition of the synovial fluid aspirate can also be indicative of infection, for example when the synovial leukocyte count and the percentage of polymorphonuclear neutrophils are elevated or when the leukocyte esterase is positive.[35] Culturing the synovial fluid or synovial tissue can identify infection when turning positive after several days to two weeks.[35] However, the sensitivity and specificity of standard tissue cultures are low, as they are reported to be 57-61% and 97-99% respectively.[37, 38] This makes it impossible to definitely exclude infection as a cause of pain or loosening after primary knee arthroplasty only based on a negative culture result.[39, 40] The percentage of 'culture negative infection cases' in published cohort studies is reported up to 22% of included cases, which is exemplary for this diagnostic dilemma.[41] Determining the alpha-defensin level in the synovial fluid provides a high specificity for prosthetic joint infection of over 90%, which is comparable to the far less expensive leucocyte esterase test.[42] However also several adverse local tissue reactions secondary to non-infectious causes such as wear particles can give false-positive results of the α-defensin test result.[43] Sonication of removed prosthetic materials has been advocated to improve the postoperative culture results.[44-49] Furthermore, Li et al show promising results of the diagnostic value of sonication fluid in blood culture bottles.[50] Another possible alternative is next generation sequencing of synovial fluid.[43] Tarabichi et al indicate that this method can identify prosthetic joint infection in both culture positive as culture negative samples.[51] Mariaux et al report that performing PCR on the sonication fluid of extracted material did not improve the bacterial detection and did not help to predict whether the patient will present a persistent or recurrent infection.[52] There are several radiologic and nuclear imaging modalities available that can be helpful to differentiate between the different causes of a patients' complaints. Plain radiographs can show loosening of an implant, which can be suggestive of infection. More advanced radiographic imaging modalities include the CT-scan, the PET-scan, the leukocyte scan and the bone scan. Even though all these modalities can hint towards infection, radiology

alone does not confirm or preclude infection as the origin of a patients' problem.[35] In addition, radiological assessment alone will not identify the infecting microorganism. The Musculoskeletal Infection Society (MSIS), the Infectious Diseases Society of America (IDSA), the European Bone and Joint Infection Society (EBJIS) and the International Consensus Meeting have proposed criteria which can be used to qualify a patient as suspected for PJI.[32, 53, 54] Multiple positive cultures of prosthetic fluid or tissue, and the presence of a sinus tract around the prosthesis are considered to be major criteria and pathognomonic for PJI.[55] The presence of three minor criteria would also confirm the diagnosis of infection. Minor criteria are elevated serum CRP and ESR, elevated synovial white blood cell count, elevated polymorphonuclear neutrophil percentage or positive change on the leukocyte esterase test strip or α-defensin, positive histological analysis of prosthetic tissue and a single positive culture.[55]

Classification of Infection

In some patients the diagnosis of infection is clear directly at presentation. These patients present themselves with fever, a clearly swollen and inflamed joint with or without purulent wound effusion or the presence of a sinus tract and with elevated serological infection parameters. This category of infections is considered to be acute.[35] Acute infections can occur within up to two or three months after the primary surgery (early acute infection) or they occur acutely years later by hematogenous transfer from an infection focus anywhere in the body (late acute or hematogenous infection). In many patients the infection is more difficult to diagnose. In chronic infection cases, mild pain while ambulating or repetitive swelling of the joint with preserved range of motion can be the only complaints a patient has, even years after the primary surgery.[40, 56] Sometimes these issues have been present from the implantation of the joint onwards, but they can also start months or years after surgery. Obvious signs of infection such as fever, persistent hydrops, or limited range of motion can be entirely absent or they can be present infrequently and mildly. Patients in whom the infection persists after DAIR treatment for an acute infection, are also considered to be chronically infected.[35] In patients with a chronic infection, the challenge of diagnosing the patient correctly is for the orthopaedic surgeon. Erroneously diagnosing a patient as not-infected exposes the patient to increased risk of poor outcome, as it is known that prostheses with undiagnosed infection have a high risk of early failure after revision surgery.[57] On the other hand if a patient is wrongly diagnosed as infected, he will have to endure a more demanding treatment protocol than would have been justified. Whether this leads to worse outcome still has to be studied.

Treatment of infection

Classifying the patients into groups according to their type of infection is important, as the success rates for the different types of treatment vary for the different types of infections, with respect to the latter timing of the first treatment after onset of first symptoms is an important prognostic variable for outcome.[2, 57-61] Several treatment options are at hand. The latter depends on the comorbidity and thus patient (perioperative) risk after a surgical procedure. For that matter in a patient with high perioperative risk, suppressive antibiotic therapy may be an option, which has high failure rates without a surgical debridement (i.e. DAIR). Even more, this option is only possible if the patient has a well-fixed prosthesis.[62, 63] Next, there is the option to surgically debride the joint, take synovial fluid and tissue cultures, start antibiotic treatment, exchange the mobile parts and retain the fixed components of the prosthesis (debridement, antibiotics, implant retention or DAIR). DAIR procedures have 46-88% chance of eradicating the infection when performed correctly and timely.[60, 61, 64, 65] Best results are obtained when patients are treated within the first 4 weeks after the index surgery or as early as possible after the onset of symptoms in hematogenous infections.[65, 66] Finally, the most radical option is surgical removal of the implant and performing either a one-stage or a two-stage procedure or even an amputation of the limb in rare cases. Revision of the prosthesis can be performed in one stage or in two stages, and with or without the use of a local antibiotic carrier inside the hip or knee.[67] Arthrodesis and amputation are salvage solutions to save a patient's life by eliminating the infected joint from the body, with all obvious consequences of the act.[68, 69] As mentioned before, the type of infection, acute or chronic, determines which type of treatment should be discussed with the patient. In patients with an acute (either early or hematogenous) infection, a DAIR procedure can be performed. The success rate of DAIR procedures depends on case specific characteristics such as the time from primary surgery, the duration of the infection, the causative pathogen and host factors such as obesity, diabetes, kidney and liver function and ASA grade.[14, 61] For patients with a chronic infection, DAIR procedures lead to poor chance of success and therefore revision is advised in those cases.[61] The definitions of acute and chronic prosthetic joint infections, although important, are based on opinion based consensus meetings, not on evidence.[35] Nevertheless, for clinical practice it is important to recognise presence of a prosthetic joint infection as soon as possible and treat the possible micro-organism(s) as early as possible after taking multiple tissue samples for micro-organism analysis. In patients with a non-acute or "chronic" infection, currently only a surgical removal of all prosthetic components during a one- or two stage procedure can eradicate the PJI.[8, 59, 67, 70]

In the near future, induction heating of the implant in conjunction with different modalities may be an option for well-fixed implants, with promising ex-vivo results.[71, 72] One-stage revision arthroplasty consists of extraction of the infected prosthesis, extensive debridement and implantation of a new prosthesis, followed by antibiotic treatment. To be able to perform a one-stage revision procedure several conditions have to be met. The patient should be fit for surgery, and the soft tissues around the infected joint should be in good shape. Also, the causative pathogen should be susceptible to antibiotics and preferably initially be treated in a combination therapy acting at the biofilm formation (like rifampin).[73] Two-stage revision arthroplasty entails extraction of the prosthesis, extensive debridement and possibly the implantation of an antibiotic-loaded spacer during the first-stage surgery followed by some weeks of antibiotic treatment. During a second-stage procedure the spacer is extracted and a prosthesis is reimplanted, often followed by another period of antibiotic treatment. Whether or not an antibiotic-loaded interval spacer is used remains the surgeons choice, however the results of two-stage revision surgery have improved since the implementation of antibiotic-loaded spacers.[8]

Finally, depending on patient factors and type of (multi)flora of micro-organisms, which can be multi-resistant, to prevent adverse effects to patients suppressive antibiotic treatment is an option.[63]

AIMS OF THE THESIS

The work presented in this thesis aims to

1. evaluate the use of antibiotic prophylaxis for prevention of prosthetic joint infections and its effect on the risk of revision for infection:
    a. Which antibiotic prophylaxis regimens are used for primary hip and knee arthroplasty in the Netherlands? **Chapter 2**
    b. What is the optimal duration of antibiotic prophylaxis for primary hip and knee arthroplasty to prevent revision for infection? **Chapter 3**

2. assess which type of hip spacer leads to the optimal result for the patient
    a. Which types of spacers are available for two-stage revision arthroplasty? **Chapter 6**
    b. What are the patient reported outcomes and infection eradication rates of functional articulating and prefabricated hip spacers? **Chapter 7**

3. assess treatment options for prosthetic joint infections
    a. What is the infection eradication rate for Coagulase-Negative Staphylococcus, a difficult to treat causative pathogen? **Chapter 8**
    b. Is there a worse patient reported outcome after two-stage revision surgery of the knee for patients who retrospectively did not have an infection? **Chapter 9**

OUTLINE OF THE THESIS

Section 1 - Prevention of Prosthetic Joint Infection

Section 1 comprises of two chapters, describing the use of antibiotic prophylaxis to prevent the occurrence of prosthetic joint infections after primary hip or knee arthroplasty. **Chapter 2** reports on the findings of a national survey in the Netherlands, investigating the treatment protocols which are currently used at the time of primary total hip or knee arthroplasty in the Netherlands, with a focus on the perioperative antibiotic prophylaxis. We also study how early infectious complications are treated and whether or not these are registered in the Dutch National Joint Registry (Landelijke Registratie Orthopaedische Implantaten, LROI). The results of **Chapter 2** were used to study patients registered in the LROI database **(Chapter 3)**. In this study we evaluated whether the type and duration of antibiotic prophylaxis administered during primary hip or knee arthroplasty was related to the number of revisions for infection within one year after primary surgery. All 242,179 patients registered in the LROI between 2011 and 2016 were included in the study.

Section 2 - Searching for evidence: Proceedings of the International Consensus Meeting on Musculoskeletal Infections

This section comprises of two chapters describing the outcomes of the International Consensus Meeting in Philadelphia in 2018. **Chapter 4** evaluated the treatment algorithm for acute infections of the hip and knee. A consensus on treatment for early and hematogenous infections was made, whether treatment should be different in septic patients, treatment options for patients with persistent wound leakage, and how bilateral infections should be treated.

For **Chapter 5** we discussed the treatment options for two-stage revision surgery of an infected hip- and knee prostheses. Consensus was made on: the optimal timing of the second stage reimplantation; whether or not all cement should be removed; whether cement should be removed from difficult anatomic positions such as intrapelvical

extruded cement; and if non-antibiotic impregnated allograft bone has an effect on recurrence of PJI after second-stage surgery.

Section 3 - The Functional Articulating Antibiotic-Loaded Hip Spacer

In case of chronic infection of a total hip prosthesis, removal of the prosthesis using a two-staged approach is merited. During the interval between the two stages an antibiotic-loaded spacer can be used to optimize functional outcome for the patient. Several types of antibiotic loaded hip spacers are available, such as prefabricated spacers and functional articulating spacers. We studied which type of spacer leads to the best infection eradication rate and functional outcome **(Chapter 6)**. In **Chapter 7** we describe our experience using a functional articulating antibiotic-loaded spacer in the treatment of prosthetic joint infections on the hip, with special emphasis on patient reported outcome, the infection eradication rate and the occurrence of complications.

Section 4 - Treatment of Prosthetic Joint Infections

Section 4 consists of two chapters. **Chapter 8** describes the infection eradication rate, patient reported outcome and complications after two-stage treatment for Coagulase-Negative Staphylococcus infection of a hip or knee prosthesis. Finally, we evaluate outcome of patients after a two-stage revision of the knee, who had initially a low suspicion of PJI. We report a case-control analysis comparing these patients to a matched cohort of patients treated with one-stage revision surgery for aseptic implant loosening **(Chapter 9)**.

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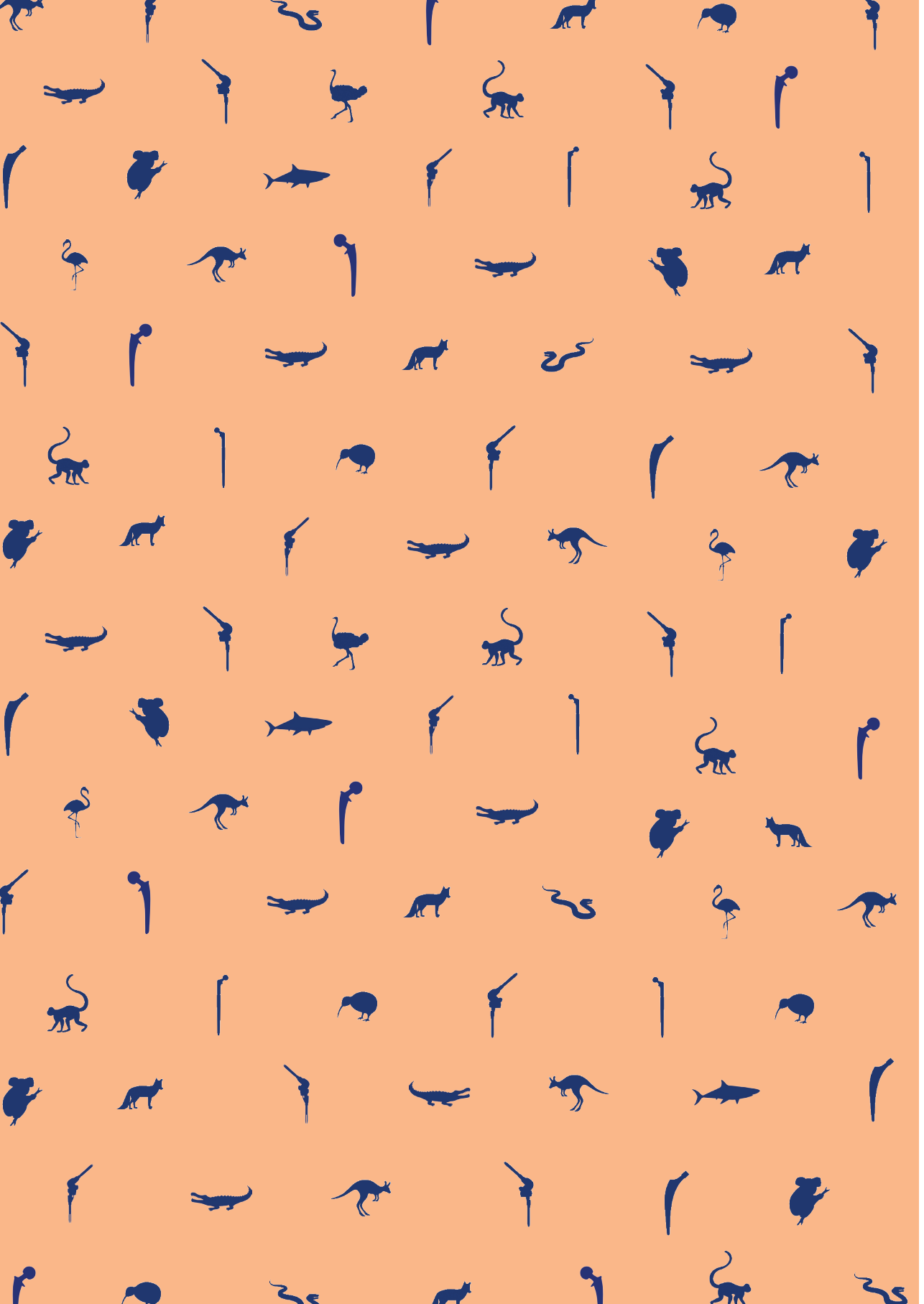
SECTION 1



CHAPTER

2

Antibiotic Prophylaxis And DAIR Treatment In Primary Total Hip And Knee Arthroplasty, A National Survey In The Netherlands

(The Journal of Bone and Joint Infection. 2018; 3(1): 5-9.)

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ABSTRACT

Background To prevent postoperative infection the use of systemic antibiotic prophylaxis is common ground. Type of antibiotic used and duration of prophylaxis are subject to debate. In case of suspected early periprosthetic infection a debridement, antibiotics and implant retention (DAIR) procedure is treatment of first choice.
This study evaluated the antibiotic prophylaxis and DAIR treatment protocols nationwide as well as reporting of these DAIR procedures to the national joint registry.

Methods All institutions that performed total hip or knee arthroplasty were contacted to complete a 16-question online survey. Questions included availability of a protocol, type and duration of antibiotic prophylaxis used and tendency to register infectious complications in the Dutch Arthroplasty Register.

Results All ninety-nine consulted institutions responded to this survey. All but one institutions have a standardized hospital based protocol for antibiotic prophylaxis in primary total hip or knee arthroplasty. Cefazolin was antibiotic prophylaxis of choice in ninety-four institutions for both primary hip and knee arthroplasty. In ten institutions one preoperative gift of antibiotic prophylaxis was administered.
A protocol describing treatment when suspecting early periprosthetic joint infection was present in seventy-one institutions. When performing a DAIR procedure modular parts were exchanged in seventy institutions in case of a hip prosthesis and in eighty-one institutions in case of a knee prosthesis. Sixty-three institutions register DAIR procedures in the Dutch Arthroplasty Register.

Interpretation In contradiction to the results of a recent study in Great Britain, we have found only little variety in availability of protocols and in the type of antibiotic used as prophylaxis in primary total hip and knee arthroplasty in The Netherlands.
Not every institution has a protocol for treatment in suspicion of early infection. Although mobile parts are exchanged in the majority of cases, there appears to be an underreporting of DAIR procedures in the Dutch Arthroplasty Register.

Keywords: antibiotic prophylaxis, national joint registry, total hip arthroplasty, total knee arthroplasty, DAIR procedure, periprosthetic joint infection.

INTRODUCTION

Total hip and knee arthroplasty (THA and TKA) are well-proven solutions in case of end-stage osteoarthritis of hip and knee.[1-5] Although, presence of complications can be devastating for the patient, especially periprosthetic joint infection (PJI).[6-8] To prevent PJI, antibiotic prophylaxis regimens are regularly used.[7, 9-11] Since the introduction of systemic and local antibiotic prophylaxis in primary THA and TKA the percentage of infectious complications has decreased to 1-2% of these arthroplasty patients.[7] A major part of PJI are caused by Staphylococcus species, particularly Staphylococcus (S.) aureus and coagulase negative staphylococci (CoNS).[6, 12] Generally these bacteria are susceptible to cephalosporins such as cefazolin or cefuroxime.[13]

The numbers of yearly performed THA and TKA are expected to increase.[14] Therefore the absolute number of infectious complications will likely increase as well, even when the percentage of infections can be limited further. Evidence based guidelines for the treatment of PJI are needed to face this challenge.[15]

A worldwide consensus meeting concerning prevention, diagnosis and treatment of periprosthetic joint infections held in 2013 suggested antibiotic prophylaxis to be discontinued within 48 hours postoperatively.[10, 16, 17] A recently updated guideline by the Netherlands Orthopaedic Association (NOV) advises an antibiotic prophylaxis to be discontinued within 24 hours after surgery.[18] Continuation of antibiotic prophylaxis for more than 24 hours postoperatively does not provide lower infection rates.[19]

The duration of systemic antibiotic prophylaxis and the type of antibiotic used remain subject of discussion. The aforementioned consensus meeting suggests a first- or second-generation cephalosporin as antibiotic of first choice.[16] The same was recommended in the recently updated guideline of the NOV.[18] A recent study performed in Great Britain revealed a wide variety of types of antibiotics used, without region-specific bacterial occurrence to account for differences in treatment.[20] This variety in treatment protocols may be caused by the absence of a national antibiotic prophylaxis guideline for all National Health Service Trusts in the UK.[20] The optimal duration of antibiotic prophylaxis remains undetermined.

In case of early infection after total hip or knee arthroplasty management with a debridement, antibiotics and implant retention (DAIR)procedure is the first treatment of choice.[21] According to the Dutch Arthroplasty Register (LROI) these procedures should be registered in the database as a revision procedure. Several studies of the National

Joint Registries in Sweden, Denmark and Norway suggest about 30-40% of PJI and DAIR-procedures are not reported in national databases.[22-25] Underreporting of infections in implant registries is likely to be caused by the design of these databases which is not adequate for registry of infections, as the reason for revision is registered preoperatively while the diagnosis of infection can only be made after results of preoperatively taken tissue cultures are complete 2-7 days later.[22] Chronic infections which are treated with antibiotic suppression therapy are also not registered in implant registries.

This study was performed to evaluate the use of standardized protocols on systemic antibiotic prophylaxis for primary THA and TKA in The Netherlands. Second, this study evaluated protocols concerning DAIR procedures and the tendency to register DAIR-procedures in the database by Dutch orthopaedic institutions. We hypothesized that, in contrast with British practice, little variety in type of antibiotics and variation in duration of antibiotic prophylaxis would exist in The Netherlands. Secondly, we hypothesized that not all DAIR treatments are performed according to a set protocol and that DAIR procedures are under-reported in the LROI.

METHODS

A list of institutions performing THA and/or TKA was retrieved from the LROI annual report 2014.[26] In each institution an orthopaedic surgeon was selected, who was specialised in either knee or hip arthroplasty. An electronic 16-question survey (Appendix I) concerning the perioperative protocol for THA and TKA was constructed and sent to the selected orthopaedic surgeons. Non-responding institutions were contacted by telephone and the survey was taken from the attending orthopaedic surgeon to assure an optimal response rate. During the period of May through July 2016 a total of ninety-nine university hospitals, teaching and regional hospitals and private orthopaedic clinics were included.

Data management and analysis were performed with SPSS 2016 software.

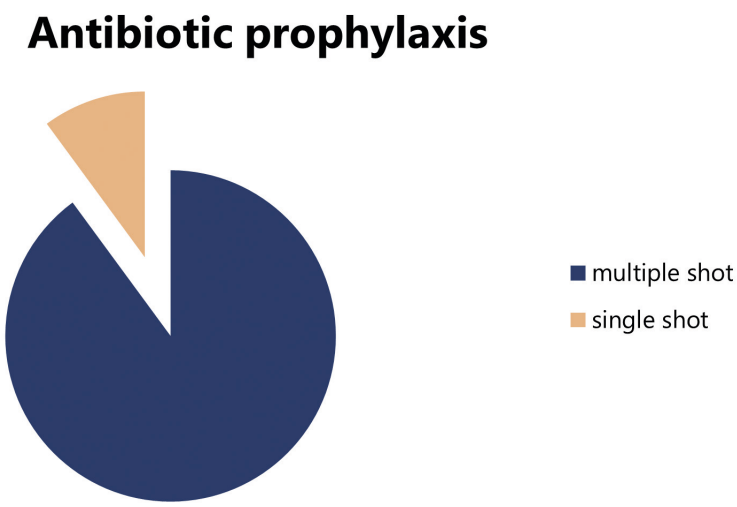
RESULTS

All ninety-nine contacted institutions completed the questionnaire. All responders were orthopaedic surgeons, practicing in eight university hospitals, eighty general hospitals and eleven private orthopaedic clinics.

Systemic antibiotic prophylaxis

A protocol describing perioperative care including systemic antibiotic prophylaxis was present in all but one institution. In eighty-nine institutions, multiple doses of antibiotic prophylaxis were administered (three or four doses in case of cefazolin, three doses in case of cefuroxime) within twenty-four hours postoperatively. Antibiotic prophylaxis was limited to a single preoperative administration in ten institutions (Figure 1). Antibiotic of choice was cefazolin in ninety-four institutions. Four institutions administered cefuroxime as antibiotic prophylaxis, one institution administered one shot of cefazolin preoperatively and two shots of cefuroxime postoperatively. Allergy for cephalosporins or proven colonization with multi-resistant micro-organisms were reported as reason for alternative prophylaxis, in which the recommendations of the international consensus meeting were followed and either clindamycin or vancomycin were administered as second-choice antibiotic.

Figure 1: Antibiotic prophylaxis

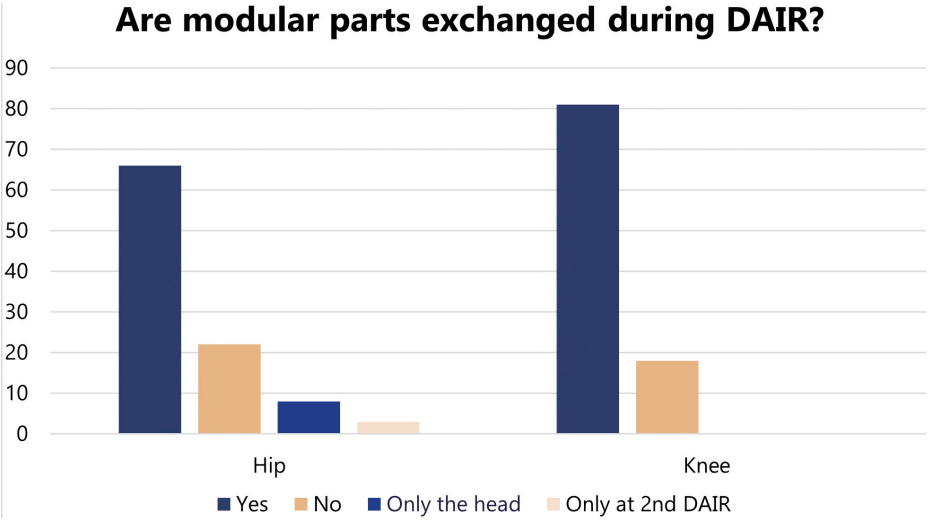


Infection treatment: Hip

Seventy-one institutions have a protocol describing the treatment for patients with suspected early periprosthetic joint infection of the hip. When a debridement, antibiotics and implant retention (DAIR) procedure is performed, modular parts are exchanged in sixty-six institutions (Figure 2). Eight institutions reported only to exchange the femoral head, but not the acetabular liner. In four of these institutions, this was motivated by the use of a monoblock acetabular component. Three institutions

only exchanged modular parts in case a second DAIR procedure was performed. In twenty-two institutions, modular parts are not exchanged during DAIR. Although many institutions exchange modular parts, DAIR procedures are registered in the LROI by only sixty-three institutions.

Figure 2: Exchange of modular parts



Infection treatment: Knee

Seventy-three institutions have a protocol describing the treatment for patients with suspected early periprosthetic joint infection of the knee. When a DAIR procedure is performed, the insert is exchanged in eighty-one institutions, the insert is not exchanged in the remaining eighteen institutions (Figure 2). DAIR procedures are registered in the LROI by sixty-three institutions.

DISCUSSION

Duration of systemic antibiotic prophylaxis remains a topic of discussion. First, we hypothesized that little variety in antibiotic prophylaxis protocols concerning primary total hip and knee arthroplasty would exist in The Netherlands. This hypothesis was correct. With all but one institutions stating the presence of a protocol for antibiotic prophylaxis in primary total hip and knee arthroplasty the authors believe this is an excellent basis for optimal prophylactic treatment in total hip and knee joint arthroplasty surgery. National and worldwide guidelines for administration of cephalosporin as antibiotic prophylaxis were followed by all Dutch institutions. The incidence of MRSA

in the Netherlands is relatively low comparing to other European countries.[12, 12, 27, 28] Therefore a prophylaxis regimen with only a cephalosporin is sufficient.[12, 27]

The duration of antibiotic prophylaxis for primary total joint arthroplasty surgery in The Netherlands is twenty-four hours in 89 out of 99 institutions. In 10 out of 99 institutions antibiotic prophylaxis consists of a single preoperative shot. Engesaeter and colleagues have found less infection and aseptic loosening after multiple shot antibiotic prophylaxis compared to single shot antibiotic prophylaxis in their observational study.[19] Up to date insufficient evidence is available to favour either one of these protocols.

The cornerstone in the treatment of PJI should be evidence based treatment protocols.[16] Protocolled care is expected to minimise the chance of errors during treatment.[16, 29] Availability of such local protocols when suspecting PJI is 71 and 73 out of 99 institutions for hip and knee arthroplasties respectively in The Netherlands. The Netherlands Orthopaedic Association (NOV) has recently updated its treatment recommendations in presence of PJI.[29] The NOV recommendation suggests exchange of all modular parts of a total joint implant in case a DAIR procedure is performed. This is in concordance with the recommendations of the international consensus meeting.[16] Exchange of modular parts during a DAIR procedure is performed in seventy-four of ninety-nine institutions in case of the hip and in eighty-one of ninety-nine institutions in case of the knee. Registration of a DAIR procedure is mandatory according to the LROI instructions on registration of revision procedures (i.e. registration would be done in case of an exchange of any implant). However, DAIR procedures are registered in the LROI by only sixty-four percent of the institutions. This means that currently there is a significant under registration, with consequently a potential underestimation of the rate of implant-related infections in our nationwide joint registry. It should be taken into account that a DAIR is also performed for prolonged wound drainage after a primary joint arthroplasty and is thus not always identical to a PJI. The possibility to register a DAIR procedures as such instead of as a partial revision may lead to improved registration of these procedures, especially in hospitals where modular parts are not exchanged during DAIR. Nevertheless, registration of DAIR procedures require better attention. First to relate DAIR procedures to primary surgery, secondly to relate them to (suspected) early and late infections resulting in implant removal. The latter can be early or late after the initial DAIR procedure, these data can then be used as part of a quality surveillance systems to improve patient care.

Weaknesses of this study are caused by its design, a questionnaire survey. Despite presence of a protocol, still differences between orthopaedic surgeons within the same institute might occur, the latter cannot be accounted for in this study. But since prevention of a PJI by antibiotic prophylaxis is common practice, the likelihood of not conferring to the prophylaxis protocol is highly unlikely. As for DAIR procedures, larger inter-surgeon variation may exist. Due to the present form of the LROI registry it has a reporting bias for PJI, which makes it difficult to draw conclusions concerning postoperative infections.

We have managed to achieve an excellent response rate, which is a pearl of this study. This study provides a perspective on the use of current prophylactic regimes and availability of protocolled care in The Netherlands. Also, the availability and characteristics of protocols describing treatment when suspecting early infection after primary hip or knee prosthesis are evaluated.

With the number of primary prosthesis expected to increase in years to come, the orthopaedic society faces a tremendous challenge. Even if the percentage of infectious complications can be decreased, the absolute number of PJI is likely to increase drastically. To cope with this challenge, research studying the optimal prevention of infectious complications, of which is also DAIR in presence of persistent wound leakage, following total hip or knee arthroplasty is crucial. Future research should show which type and duration of antibiotic prophylaxis regime provides lowest risk for infection after primary total hip or knee arthroplasty.

CONTRIBUTION OF AUTHORS

All authors contributed to study design and draft and/or revision of the manuscript. Data collection and analysis were performed by ESV.

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CONFLICT OF INTEREST AND FUNDING

We have no conflict of interest to mention. No funding was received for this study.

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APPENDIX 1

Questionnaire

General information

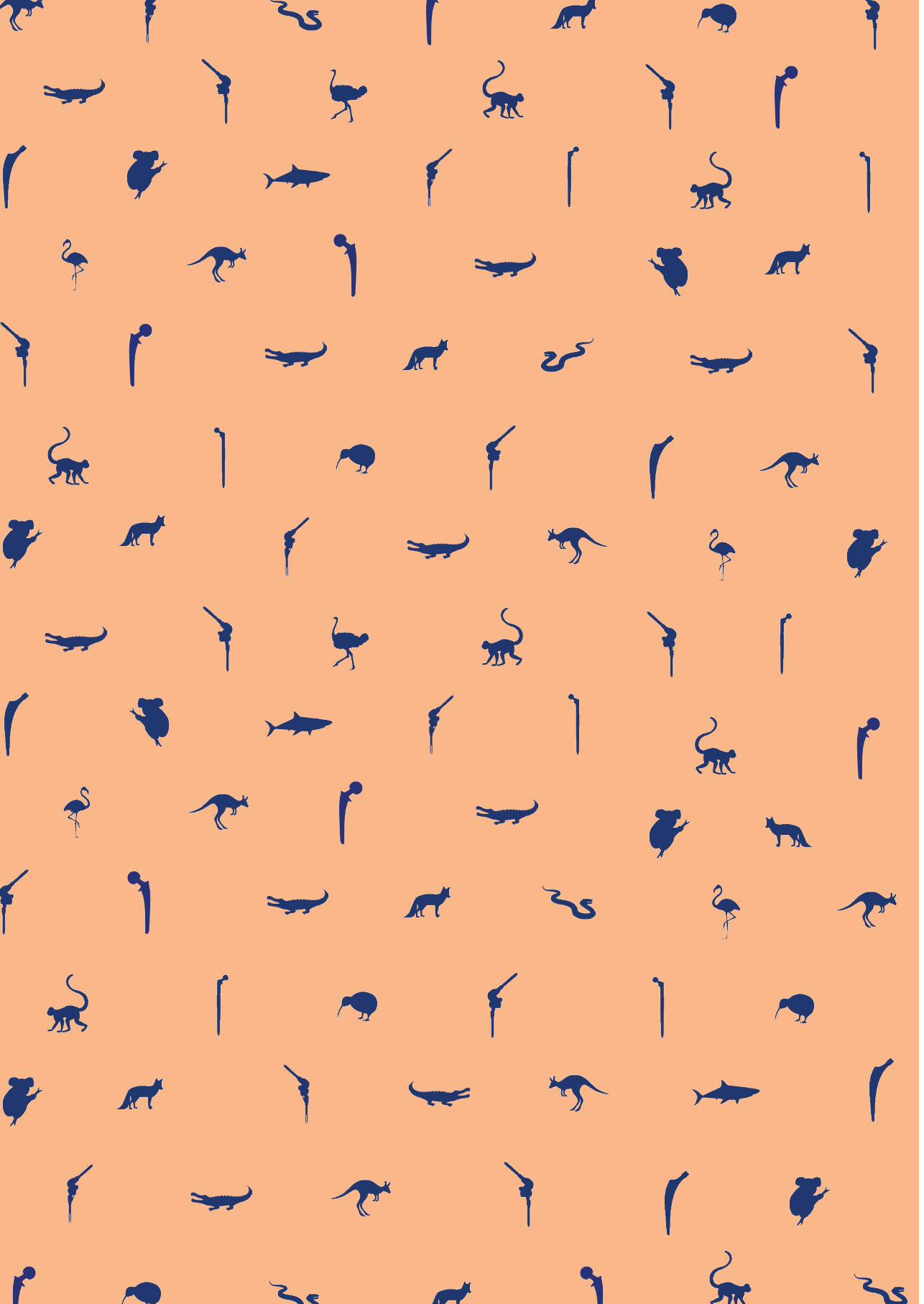
1. What is your profession?
2. In which institution are you employed?

Hip

3. Is a set protocol used for perioperative management concerning THA?
4. Which systemic antibiotic is used as prophylaxis in primary THA?
5. How many doses of antibiotic prophylaxis are administered in primary THA?
6. Does the protocol describe reasons to deviate from standard antibiotic prophylaxis?
7. Does your institution have a set protocol to be used in case of suspected early infection?
8. In case of DAIR procedure, are modular parts exchanged?
9. In case of DAIR procedure, is this procedure registered in the Dutch national joint registry database?

Knee

10. Is a set protocol used for perioperative actions concerning TKA?
11. Which systemic antibiotic is used as prophylaxis in primary TKA?
12. How many doses of antibiotic prophylaxis are administered in primary TKA?
13. Does the protocol describe reasons to deviate from standard antibiotic prophylaxis?
14. Does your institution have a set protocol to be used in case of suspected early infection?
15. In case of DAIR procedure, are modular parts exchanged?
16. In case of DAIR procedure, is this procedure registered in the Dutch national joint registry database?



CHAPTER

3

Similar risk of complete revision for infection with single-dose versus multiple-dose antibiotic prophylaxis in primary arthroplasty of the hip and knee: results of an observational cohort study in the Dutch Arthroplasty Register in 242,179 patients

(Acta Orthopaedica. 2020 Jul 23:1-7.)

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ABSTRACT

Background and purpose

The optimal type and duration of antibiotic prophylaxis for primary arthroplasty of the hip and knee are subject to debate. We compared the risk of complete revision (obtained by a 1- or 2-stage procedure) for periprosthetic joint infection (PJI) after primary total hip or knee arthroplasty between patients receiving a single dose of prophylactic antibiotics and patients receiving multiple doses of antibiotics for prevention of PJI.

Methods A cohort of 130,712 primary total hip and 111,467 knee arthroplasties performed between 2011 and 2015 in the Netherlands was analysed. We linked data from the Dutch arthroplasty register to a survey collected across all Dutch institutions on hospital-level antibiotic prophylaxis policy. We used restricted cubic spline Poisson models adjusted for hospital clustering to compare the risk of revision for infection according to type and duration of antibiotic prophylaxis received.

Results For total hip arthroplasties, the rates of revision for infection were 31/10,000 person-years (95% CI 28–35), 39 (25–59), and 23 (15–34) in the groups that received multiple doses of cefazolin, multiple doses of cefuroxime, and a single dose of cefazolin, respectively. The rates for knee arthroplasties were 27/10,000 person-years (95% CI 24–31), 40 (24–62), and 24 (16–36). Similar risk of complete revision for infection among antibiotic prophylaxis regimens was found when adjusting for confounders.

Interpretation In a large observational cohort we found no apparent association between the type or duration of antibiotic prophylaxis and the risk of complete revision for infection. This does question whether there is any advantage to the use of prolonged antibiotic prophylaxis beyond a single dose.

INTRODUCTION

Annually around 1 million patients receive a total hip or total knee prosthesis in the United States and over 190,000 hip and knee replacements are performed in England and Wales.[1, 2] The incidences of prosthetic replacement of the hip and knee are expected to increase.[3] Prosthetic joint infection (PJI) following total hip or knee arthroplasty and the treatment thereof are catastrophic for patients and pose tremendous costs to healthcare systems.[4-6] Perioperative antibiotic prophylaxis remains an effective method of reducing the risk of PJI.[7, 8] The type and duration of antibiotic prophylaxis are subject to debate.

Both single dose and multiple dose antibiotic prophylaxis regimens have been advocated with comparable results.[8, 9] The recommendations provided by the Second International Consensus Meeting of the MusculoSkeletal Infection Society (MSIS) and the European Bone and Joint Infection Society (EBJIS) advise that antibiotic prophylaxis should be administered 30-60 minutes before incision and discontinued within 24 hours after surgery.[10, 11] Large variations in prophylaxis regimens has been observed in the United Kingdom.[12] The Dutch national orthopaedic association advises administration of antibiotic prophylaxis using a first or second generation cephalosporin starting 30-60 minutes preoperatively and discontinuing the antibiotic prophylaxis within 24 hours.[13, 14] The World Health Organisation and, in the USA, the Center for Disease Control and Prevention (CDC) recommends against the use of postoperative continuation of antibiotic prophylaxis and advocate for a single dose of antibiotics delivered pre-operatively.[15] This recommendation is vehemently challenged by the American Association of Hip and Knee Surgeons and the International Consensus Meeting which encourage their members to proceed with the current common practice of multiple dose antibiotic prophylaxis protocols until more evidence is available.[16]

We compared the risk of complete revision for infection in the 1st year following primary hip and knee arthroplasty according to the perioperatively administered antibiotic prophylaxis regimen by using data from the Dutch Arthroplasty Register (LROI).

METHODS

This study was structured using the STROBE guideline. In this observational cohort study, we report analyses of data for the Netherlands from the Dutch Arthroplasty Register (LROI) between January 1st 2011 and December 31st 2015. We included all patients who had a primary hip or knee replacement during this period in the study. Patient consent was obtained for data collection and linkage by the LROI. Using data on patient level was not possible due to the legislation of the General Data Protection Regulation.

In absence of individual patient level data on antibiotic prophylaxis, we performed an national audit of hospital perioperative antibiotic prophylaxis regimens in the Netherlands.[17] All 99 Dutch hospitals or clinics performing primary total hip arthroplasty (THA) or total knee arthroplasty (TKA) were contacted and all completed a survey to identify existence of treatment protocols concerning primary joint replacement, existence of protocols regarding treatment strategy in case of suspected early postoperative infection and tendency to register procedures in the LROI database. We asked, in particular, about type and duration of antibiotic prophylaxis. This survey showed a variance in postoperative duration of antibiotic prophylaxis. 10 Dutch hospitals administered a single shot antibiotic prophylaxis, while the remaining 89 administered a multiple shot antibiotic prophylaxis. This variance facilitated an observational cohort study using the LROI. The LROI has a completeness of over 95% for primary hip and knee arthroplasties and of 91% and 92% for the hip and knee revision procedures respectively.[18-20] The translated survey form can be found in Appendix 1, supplementary data.

Each patient who had a primary THA or TKA was followed up for a minimum of 12 months until the end of the observation period (December 31st, 2015) or until the date of 1- or 2-stage revision for infection, revision for another indication, death or end of follow-up (January 1st 2018). Revisions for infection included only complete revision of the total system, obtained by a 1- or 2-stage revision procedure. All partial revisions (e.g. debridement, antibiotics and implant retention procedures (DAIR)) were excluded because these partial revisions are inconsistently recorded compared to total revisions.[17, 18] We chose to end the follow-up period at 1 year after surgery as with longer follow-up the influence of hematogenous infections on the measured outcome may increase to become larger than the influence of the duration of antibiotic prophylaxis at primary surgery.

We defined infection status using the surgical indication reported in the LROI revision arthroplasty form following surgery by the treating orthopaedic surgeon. We included patients whom had undergone complete revision captured by the LROI where the reason for revision was defined as infection in the infected group and patients in whom the reason for revision was not reported, or reason for revision other than infection was reported, in the non-infected group. The diagnosis and treatment strategy for complete revision for infection was at the discretion of the surgeon and treating unit and it reflected contemporary practice over the study period, with raised inflammatory markers, joint specific symptoms, sinuses, and positive microbiological cultures being common diagnostic features over that period.[21]

We compared the risk of complete revision surgery for infection in the 1st year following primary arthroplasty by the type and duration of antibiotic prophylaxis regimen administered at primary surgery. We considered the patient characteristics age, sex, BMI, ASA grade, and previous surgery. We considered surgical factors such as indication for surgery, surgical approach, type of fixation and bearing surface. Data from the LROI database were combined at hospital level with the results of the national survey on antibiotic prophylaxis. Results of the survey show there were 3 types of antibiotic regimens that are used in the Netherlands: multiple dose of cefazolin (MCZ), multiple dose of cefuroxime (MCX), and single dose of cefazolin (SCZ), which are all in concordance with the Dutch guideline for perioperative antibiotics in total hip and knee arthroplasty.[17] No other antibiotic regimens were encountered in the survey. Patients were divided into 3 groups (MCZ, MCX and SCZ) according to the antibiotic prophylaxis protocol of the hospital they were treated.

Statistics

We investigated the association between hospital antibiotic prophylaxis regimen policies (MCZ used as the reference) and the risk of complete revision for infection in the first 12 months following the index primary surgery with Poisson regression to account for time at risk and to produce hazard ratios including 95% confidence intervals (CI). The baseline hazard rate was modelled with restricted cubic splines. The optimum numbers of knots (3 degrees of freedom (d.f.) for the hip models, 4 d.f. for the knee models) was identified with AIC and BIC criteria (Appendix Table 1, supplementary data). Interaction terms between the splines and the main exposure covariates were included to estimate the time-dependent hazard ratio for complete revision for infection of the different antibiotic prophylaxis regimens.[22] Huber-White-sandwich estimate of variance were computed to adjust for within-hospital correlation. The models were stratified by surgical site and adjusted for age, sex, BMI and ASA classification. Multiple imputation by chained equations (5 imputations sets) under a missing at random framework was used to account for missing data. The imputation model incorporated the PJI status, time at risk, the main exposure, the aforementioned adjustment factors and indication for surgery, surgical approach, method of fixation, bearing surface, and year of surgery as ancillary variables. All statistical analyses were performed using Stata, version 15.1.

Ethics, funding, and potential conflicts of interest

The study protocol was registered on ClinicalTrials.gov with reference NCT03348254.

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The National Institute for Health Research had no role in study design, data collection analysis, interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

RESULTS

During 2011 to 2015, 130,712 primary total hip arthroplasties and 111,467 primary total knee arthroplasties were performed across 99 centers. 399 hips and 303 knees were revised within 1 year of the primary arthroplasty for an indication of infection (Tables 2 and 3, see supplementary data). Multiple dose cefazolin (MCZ), multiple dose cefuroxime (MCX), or single dose cefazolin (SCZ) antibiotic prophylaxes were respectively administrated to 87%, 4% and 9% of patients. Hereafter, 'revision' refers to '1 and 2-stage revisions'.

For total hip arthroplasties, the 1-year rates of revision for infection (CI) were respectively 31/10,000 person-years (28-35), 39 (25-59), and 23 (15-34) in the groups that received MCZ, MCX, and SCZ; the rates for knee arthroplasties were 27 (24-31), 40 (24-62), and 24 (16-36) respectively. The rates of revision for infection over time according to antibiotic prophylaxis regimen are shown in Figures 1 and 2. Revision for infection was performed most frequently in the first 3 months postoperatively for both hip and knee replacements.

While the risk of complete revision for infection appeared to differ over time, no or little evidence of differences between antibiotic prophylaxis regimens were found (Figures 3 and 4). In the first 11 months after primary hip arthroplasty, the risk of revision was comparable between SCZ and MCZ (adjusted $HR_{SCZ\ vs.\ MCZ}$ at 3 months 0.59 [0.19-1.79], at 6 months 1.02 [0.43-2.39]), but the risk of revision was higher in the SCZ group thereafter (HR 2.21 [1.12-4.38]). No evidence of difference was found between MCZ and MCX following hip arthroplasty (adjusted $HR_{MCX\ vs.\ MCZ}$ at 3 months 1.54 [0.77-3.08], at 6 months 1.00 [0.60-1.68], at 12 months 0.61 [0.20-1.81]). For patients receiving a primary total knee arthroplasty revision rates between SCZ and MCZ were comparable (adjusted $HR_{SCZ\ vs.\ MCZ}$ at 3 months 1.81 [0.87-3.76], at 6 months 0.89 [0.15-5.31], at 12 months 0.47

[0.09-2.37]). The risk of revision for infection was also comparable between MCZ and MCX (adjusted $HR_{MCX\ vs.\ MCZ}$ at 3 months 1.71 [0.54-5.37], at 6 months 1.15 [0.65-2.02], at 12 months 1.88 [0.56-6.31]). The patterns observed were comparable in the unadjusted and adjusted models (Tables 1 and 2).

Figure 1: Rate of complete revision for infection in the first 12 months following primary hip replacement by type of antibiotics regimen.

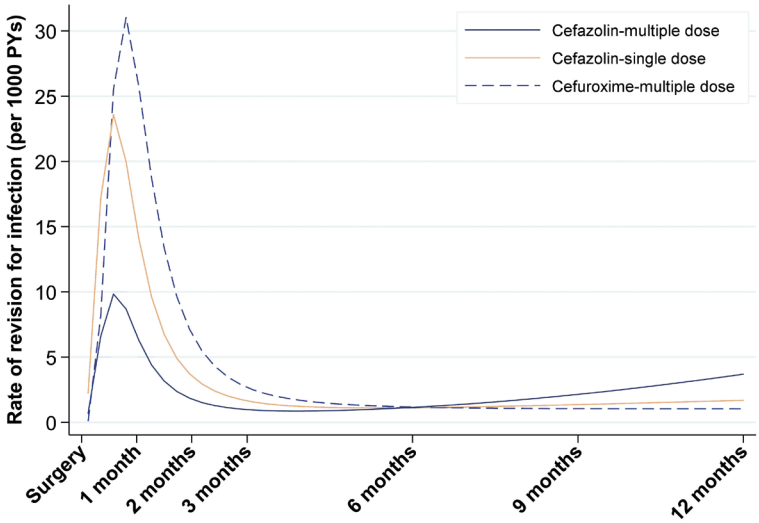

Figure 2: Rate of complete revision for infection in the first 12 months following primary knee replacement by type of antibiotics regimen.

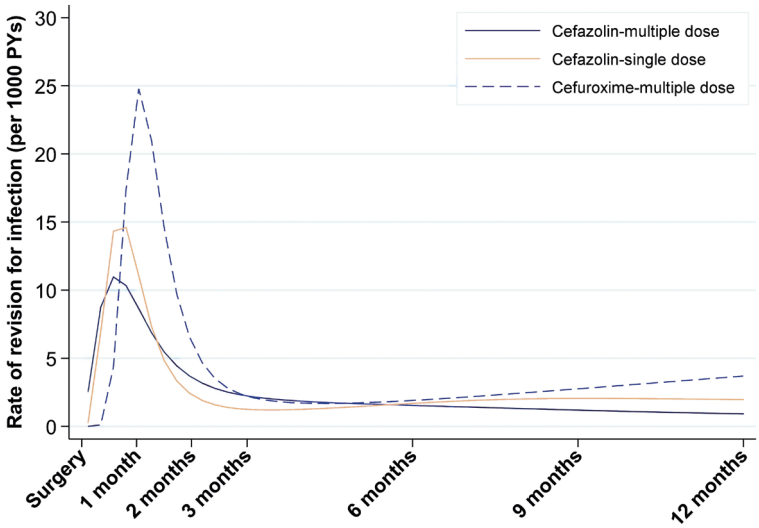

Figure 3: Hazard ratio and 95% CI* of complete revision for infection in the first 12 months following primary hip replacement by type of antibiotics regimen (reference: cefazolin multiple dose). *Derived from unadjusted Poisson model with restricted cubic splines (3 degrees of freedom) (see Appendix Table 2).

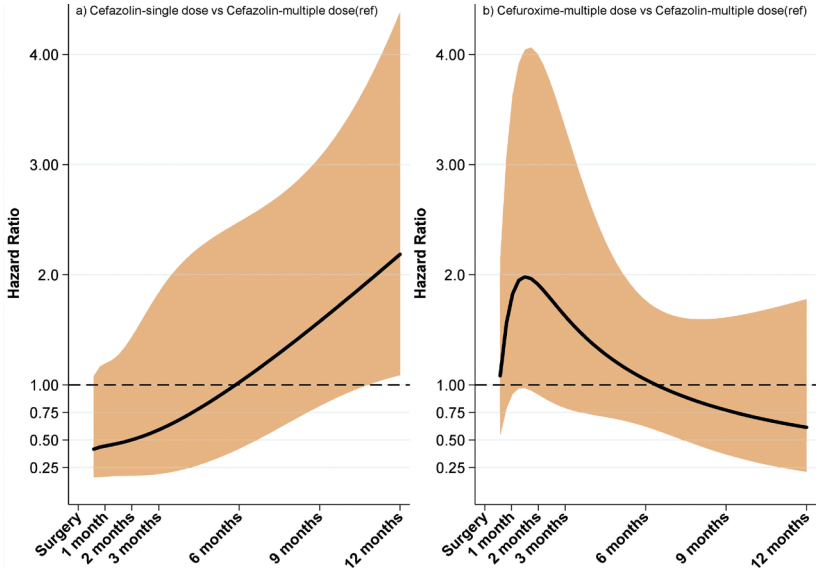

Figure 4: Hazard ratio and 95% CI* of complete revision for infection during the first 12 months following primary knee replacement by type of antibiotics regimen (reference: cefazolin multiple dose). *Derived from unadjusted Poisson model with restricted cubic splines (3 degrees of freedom) (see Appendix Table 3).

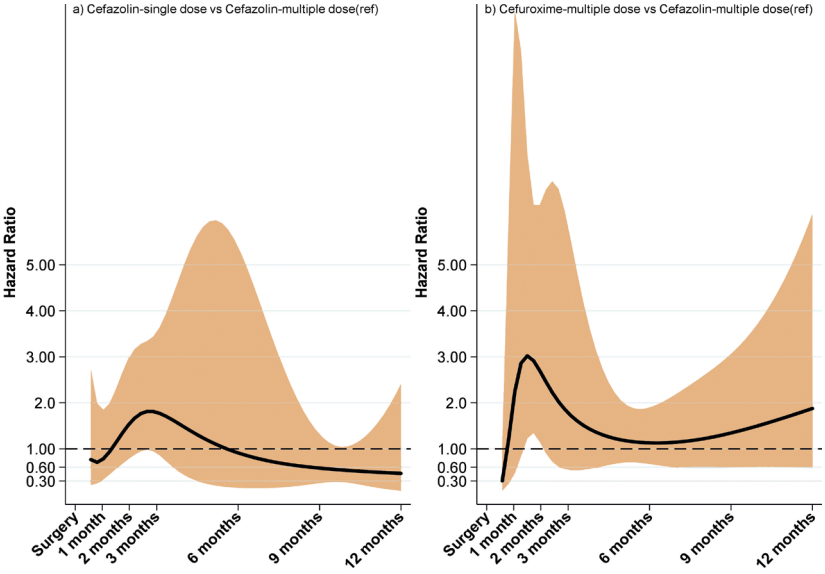

Table 1: Unadjusted Hazard-Ratio (HR) of revision for PJI infection in the first 12 months following primary hip replacement (Reference: Cefazolin multiple dose)

Time*	HR $_{\text{Cefazoline-single dose}}$	95%CI	HR $_{\text{Cefuroxime-multiple dose}}$	95%CI
1 month	0.45	[0.17, 1.20]	1.82	[0.92, 3.62]
2 months	0.50	[0.17, 1.42]	1.92	[0.92, 4.01]
3 months	0.60	[0.19, 1.87]	1.59	[0.78, 3.25]
6 months	1.04	[0.43, 2.49]	1.03	[0.61, 1.74]
9 months	1.59	[0.82, 3.09]	0.76	[0.36, 1.61]
12 months	2.18	[1.09, 4.38]	0.61	[0.21, 1.78]

*Time from primary procedure

Adjusted Hazard-Ratio (HR)** of revision for PJI infection in the first 12 months following primary hip replacement (Reference: Cefazolin multiple dose)

Time*	HR $_{\text{Cefazoline-single dose}}$	95%CI	HR $_{\text{Cefuroxime-multiple dose}}$	95%CI
1 month	0.45	[0.17, 1.20]	1.80	[0.92, 3.52]
2 months	0.49	[0.17, 1.38]	1.88	[0.92, 3.86]
3 months	0.59	[0.19, 1.79]	1.54	[0.77, 3.08]
6 months	1.02	[0.43, 2.39]	1.00	[0.60, 1.68]
9 months	1.59	[0.83, 3.02]	0.75	[0.35, 1.61]
12 months	2.21	[1.12, 4.38]	0.61	[0.20, 1.81]

*Time from primary procedure, **adjusted for age, sex, BMI and ASA grade

Table 2: Unadjusted Hazard-Ratio (HR) of revision for PJI infection in the first 12 months following primary knee replacement (Reference: Cefazolin multiple dose)

Time*	HR $_{\text{Cefazoline-single dose}}$	95%CI	HR $_{\text{Cefuroxime-multiple dose}}$	95%CI
1 month	0.78	[0.33, 1.84]	2.24	[0.48, 10.52]
2 months	1.52	[0.78, 2.95]	2.70	[1.15, 6.30]
3 months	1.77	[0.86, 3.63]	1.72	[0.54, 5.50]
6 months	0.89	[0.15, 5.26]	1.13	[0.66, 1.91]
9 months	0.58	[0.26, 1.26]	1.36	[0.59, 3.11]
12 months	0.47	[0.09, 2.40]	1.88	[0.58, 6.10]

*Time from primary procedure

Adjusted Hazard-Ratio (HR)** of revision for PJI infection in the first 12 months following primary knee replacement (Reference: Cefazolin multiple dose)

Time*	HR $_{\text{Cefazoline-single dose}}$	95%CI	HR $_{\text{Cefuroxime-multiple dose}}$	95%CI
1 month	0.78	[0.33, 1.83]	2.34	[0.49, 11.20]
2 months	1.55	[0.80, 3.02]	2.70	[1.16, 6.29]
3 months	1.81	[0.87, 3.76]	1.71	[0.54, 5.37]
6 months	0.89	[0.15, 5.31]	1.15	[0.65, 2.02]
9 months	0.58	[0.26, 1.28]	1.38	[0.58, 3.30]
12 months	0.47	[0.09, 2.37]	1.88	[0.56, 6.31]

DISCUSSION

In this large observational cohort study of primary total hip and knee replacement, our findings suggest a comparable risk of complete revision for infection between the antibiotic prophylaxis regimens in terms of type of antibiotic and duration of prophylaxis during the first 12 months following surgery. When examining the hazard ratios, it is important to note that the majority of infections occurred within the first 3 months of surgery. Comparing single and multi-dose prophylaxis with Cefazolin for hip replacement, the hazard ratio for complete revision for infection following single dose prophylaxis steadily increased over time from less than half of that with multi-dose to over double the incidence of infection by month 12. It may be due to low virulence micro-organisms that are more susceptible to multi-dose therapy presenting with infection later. In case this is true, the differences between the different regimes should become more apparent with longer follow-up. This was not the case following knee replacement and alternatively may simply reflect either a chance occurrence, differences in patient- and surgery related factors, or residual confounding. Adjustment for established confounding variables (age, sex, BMI, ASA grade) did not change these results.

We observed that the highest risk of complete revision for infection in the year following surgery occurred within the first 3 months after the operation. Rates then appear to rise again towards the end of the follow up period. These patterns are consistent with contemporary patterns found in other registries.[23-25] This may be due to the effect of more virulent microorganisms presenting during the first 3 months and less virulent microorganisms presenting later. Since the LROI does not provide data on which microorganism is causing the PJI, this remains speculative. Another reason might be a genuine increase in the incidence of PJI or may reflect more rapid diagnosis and aggressive treatment of PJI in recent years. We have not analysed procedures where only debridement or partial revision (including debridement and implant retention (DAIR) with modular exchanges) were performed as these procedures are not reliably captured by the LROI registry.[17] DAIR has been shown to effectively treat infection in approximately 46-76% of cases.[26] We have no reason to believe that the use of DAIR is related to type or duration of antibiotic prophylaxis, but it is a possible cause of residual confounding.

It has been suggested that the most appropriate perioperative prophylactic antibiotic is a first or second generation cephalosporin (i.e. cefazolin or cefuroxime) administered intravenously within 30 to 60 minutes prior to incision as single and weight adjusted dose.[27-29] This policy is part of antibiotic stewardship, performed in countries with a

low prevalence of MRSA.[7, 30] While consensus exists on type of antibiotic prophylaxis, the postoperative duration of antibiotic prophylaxis remains subject to discussion.[11]

A recent systematic review and meta-analysis by Thornley et al. (2015) explored whether or not a single preoperative antibiotic dose is adequate for arthroplasty patients.[8] The review included 4 RCTs including 4,036 patients.[31-34] They concluded that additional postoperative antibiotic doses did not reduce the rates of infections (3.1% versus 2.3% postoperative PJI for multiple dose and single dose prophylaxis respectively). However, they reported that the quality of the included studies was very low. 3 of these studies were performed more than 20 years ago, while the other study used Teicoplanin, which is no longer recommended for use as antibiotic prophylaxis.[34] Heydemann and Nelson (1986) randomised 211 patients between single dose and 48-hour multiple dose prophylaxis, but found no cases of PJI in either group.[31] Ritter et al. (1989) compared a single dose of cefuroxime to 24 hours of postoperative prophylaxis in 196 patients, and found no cases of PJI in either group.[32] Wymenga et al. (1992) randomised 3,013 patients in a multicenter RCT comparing a single preoperative dose of cefuroxime to a group receiving three doses and found no significant differences in PJI rates between groups.[33] Engesaeter et al. (2003) reported the lowest rate of infection for patients who received four doses of antibiotic prophylaxis in 24 hours, compared to patients who received one, two or three doses in their study of the Norwegian Arthroplasty Register.[35] All authors of these studies recognized their study sample to be underpowered for determining a difference in PJI rates and recommended further studies to provide a definite answer. Based on these studies, the CDC has recently recommended against the use of postoperative continuation of antibiotic prophylaxis.[15] The recent International Consensus meeting advises to continue antibiotics postoperatively for 24 hours until better quality evidence is available.[11] A protocol for a RCT randomizing patients receiving a total knee arthroplasty between single dose versus multiple dose antibiotic prophylaxis has been registered on clinicaltrials.gov (NCT03283878). The study aims to definitively answer which duration of antibiotic prophylaxis is best. However, the planned follow-up of 90 days seems too short to capture all relevant infections. Also, the sample size is not justified in the trial registration, but with the aim of including 8000 patients the study seems underpowered.

Our study has several strengths. The large numbers studied allows adequate power to detect rare outcomes such as complete revision for infection. Data capture represents over 98% of national activity.[18] This rate of coverage provides excellent external validity and generalizability of our findings. The rate of complete revision for infection within

1 year of primary arthroplasty is higher for males, patients with higher BMI, or higher ASA grade in all groups, independent of the type of antibiotic prophylaxis.[23, 36] This is in concordance with the literature and highlights the comparability of this Dutch arthroplasty cohort to other studied cohorts.[23, 36, 37]

In order to establish the current practice for antibiotic prophylaxis regimes, we conducted a comprehensive national survey to determine current practice. The outcome of interest is a binary endpoint, whilst this may mean that not all cases of PJI are captured, as many may be treated without complete revision surgery, it does make the end point easily defined.[38] In the absence of randomized controlled trials on the type and duration of antibiotic prophylaxis, this natural experiment in a large and generalizable national registry represents the best data currently available to determine if there is a difference in the risk of complete revision for infection according to the antibiotic prophylaxis regimen.

The study does have limitations. The LROI database was established as an arthroplasty register, whilst one of the outcomes of interest is complete revision for infection, the register was not designed to capture all infection outcomes and thus there is likely to be underreporting of infection as may also be the case in other national arthroplasty registries.[37, 39] The most notable effect of this is the lack of capture of further procedures performed after the primary surgery to manage infection, such as DAIR procedures. The Dutch survey showed only 64% of hospitals registered DAIR procedures in the LROI, thus we did not include these in our analysis. As about 50% of PJI may be only treated with DAIR and arthroplasty registries are known to provide an underestimation of the rate of prosthetic revisions due to PJI of 20%, we may be missing as much as 70% of all treated infections.[39, 40] Although prospectively collected, our data are observational and we can only draw conclusions on the nature and magnitude of the associations but cannot establish causative relation due to the possibility of residual confounding and estimation uncertainty. Whilst we conducted a comprehensive survey to establish the current practice in terms of antibiotic prophylaxis regimes, it is likely that for various reasons, including allergy, intolerance, and surgeons' preference, not all patients received the antibiotics as per hospital protocol. However, a recent large retrospective study in the USA showed that 95% of patients received standard antibiotic prophylaxis.[41] The three types of antibiotics all are cephalosporins with the same allergy profile, therefore the percentage of patients with allergies should be comparable in all groups. Changes to the local antibiotic protocols during the study period have not been captured by the survey. The Dutch guideline for antibiotic prophylaxis around primary

hip and knee arthroplasty did not change during the time period. However, changes to the antibiotic protocols can have occurred between the groups in all directions. Due to the quasi-randomized allocation of our patients, this should not introduce systematic bias.

Thus, this study resembles a natural experiment. Rather than controlling for observed confounders and expecting no unobserved confounders to be present (as in multiple regression, matching, and reweighting), natural experiments identify variation in the exposure, known to be independent of other confounders.[42] In our study quasi-random variation in the exposure (antibiotic prophylaxis regimen after total hip or knee arthroplasty) arises from naturally occurring random variation due to allocation of patients to the regional hospital near their residence. Natural experiments minimize the risk of confounding due to selective exposure to the intervention or residual confounding, have internal validity and transparency of assumptions.[42] To establish true causality, a superiority or non-inferiority randomized controlled trial is still needed. However, as PJI is rare, the numbers needed for such a trial would be very large. Nonetheless, as the impact of PJI is so devastating,[6] we recommend that such a trial is undertaken and suggest that embedding such a trial in a national arthroplasty registry may reduce costs and improve feasibility. Until such time, the data represented here is the best available evidence and it does question whether there is any advantage to the use of prolonged antibiotic prophylaxis beyond a single dose.

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AUTHOR CONTRIBUTIONS

ESV, EL, DJM and RWP designed the study. The data were extracted from the LROI database by Liza van Steenbergen of the LROI. ESV performed the literature search. EL performed the data analysis. All authors interpreted data, drafted, and reviewed the final manuscript. All authors approved the submitted manuscript and take responsibility for the integrity of the work.

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APPENDIX TABLES

Appendix table 1: Model fit
The models that minimised the AIC and BIC criteria were selected to identify the number of optimal knots for the spline function (number of degrees of freedom-1). The log of follow-up time was modelled to obtain better fitting models.

	d.f. [1]	AIC[2]	BIC[3]
Hip model			
	2	2570	2586
	3	***2429***	***2447***
	4	2431	2452
	5	2432	2456
Knee model			
	2	2218	2234
	3	2133	2151
	4	***2111***	***2132***
	5	2114	2139

1. Degrees of freedom
2.Akaike information criterion
3.Bayesian information criterion

Appendix Table 2: Description of hip procedures by antibiotics regimen. * Revision rate for infection per 10,000 person-years

		Cefazolin multi dose					Cefazolin single dose					Cefuroxime multi dose				
		Revision	n	Person-years	Rate*	95%CI	Revision	n	Person-years	Rate*	95%CI	Revision	n	Person-years	Rate*	95%CI
Overall		350	113285	111562	31.4	[28.2, 34.8]	26	11455	11314	23	[15, 33.7]	23	5972	5830	39.4	[25, 59.2]
Year of surgery	2011	22	20238	19986	11	[6.9, 16.7]	1	2225	2201	4.5	[0.1, 25.3]	4	1101	1075	37.2	[10.1, 95.2]
	2012	40	21580	21256	18.8	[13.4, 25.6]	3	2270	2241	13.4	[2.8, 39.1]	5	1132	1109	45.1	[14.6, 105.2]
	2013	53	22418	22080	24	[18, 31.4]	2	2225	2203	9.1	[1.1, 32.8]	4	1140	1117	35.8	[9.8, 91.7]
	2014	94	24232	23861	39.4	[31.8, 48.2]	10	2353	2324	43	[20.6, 79.1]	4	1262	1231	32.5	[8.9, 83.2]
	2015	141	24817	24379	57.8	[48.7, 68.2]	10	2382	2344	42.7	[20.5, 78.4]	6	1337	1299	46.2	[17, 100.5]
Sex	Male	173	37855	37115	46.6	[39.9, 54.1]	17	3920	3856	44.1	[25.7, 70.6]	12	2065	2003	59.9	[31, 104.7]
	Female	175	75122	74144	23.6	[20.2, 27.4]	9	7526	7448	12.1	[5.5, 22.9]	11	3898	3819	28.8	[14.4, 51.5]
	Missing	2	308	304	65.9	[8, 238]	0	9	9	0	[0, 4086.5]	0	9	9	0	[0, 4086.5]
Age	Missing	0	178	176	0	[0, 209.1]	0	4	4	0	[0, 9194.6]	0	8	7	0	[0, 5047.4]
	<60	68	19092	18859	36.1	[28, 45.7]	8	2172	2156	37.1	[16, 73.1]	5	1127	1110	45	[14.6, 105.1]
	60-65	58	19156	18936	30.6	[23.3, 39.6]	4	1889	1871	21.4	[5.8, 54.7]	8	986	968	82.7	[35.7, 162.9]
	66-70	79	21791	21536	36.7	[29, 45.7]	7	2105	2084	33.6	[13.5, 69.2]	3	1137	1114	26.9	[5.6, 78.7]
	71-75	55	21076	20809	26.4	[19.9, 34.4]	2	2143	2122	9.4	[1.1, 34.1]	3	1120	1094	27.4	[5.7, 80.1]
	76-80	56	18104	17790	31.5	[23.8, 40.9]	2	1788	1763	11.3	[1.4, 41]	3	881	848	35.4	[7.3, 103.4]
	>80	34	13888	13457	25.3	[17.5, 35.3]	3	1354	1313	22.8	[4.7, 66.8]	1	713	689	14.5	[0.4, 80.9]
BMI	Missing	91	57099	56295	16.2	[13, 19.8]	6	6344	6268	9.6	[3.5, 20.8]	10	2981	2922	34.2	[16.4, 62.9]
	<18.5	3	477	460	65.2	[13.4, 190.4]	0	40	36	0	[0, 1011.1]	0	41	37	0	[0, 991.9]
	18.5-24.9	36	17623	17346	20.8	[14.5, 28.7]	5	1639	1618	30.9	[10, 72.1]	3	1013	990	30.3	[6.3, 88.6]
	25-29.9	106	24280	23916	44.3	[36.3, 53.6]	9	2201	2175	41.4	[18.9, 78.6]	4	1208	1172	34.1	[9.3, 87.4]
	30-39.9	100	13109	12872	77.7	[63.2, 94.5]	5	1153	1140	43.9	[14.2, 102.3]	6	694	675	88.8	[32.6, 193.3]
	40+	14	697	673	208	[113.7, 349]	1	78	76	131.6	[3.3, 733.1]	0	35	34	0	[0, 1081.5]

Appendix Table 2: Description of hip procedures by antibiotics regimen. * Revision rate for infection per 10,000 person-years (continued)

		Cefazolin multi dose					Cefazolin single dose					Cefuroxime multi dose				
		Revision	n	Person-years	Rate*	95%CI	Revision	n	Person-years	Rate*	95%CI	Revision	n	Person-years	Rate*	95%CI
ASA	Missing	5	1138	1118	44.7	[14.5, 104.3]	0	333	332	0	[0, 111.1]	1	88	83	120.6	[3.1, 671.7]
	ASA I	49	23602	23411	20.9	[15.5, 27.7]	4	2428	2411	16.6	[4.5, 42.5]	3	1177	1170	25.6	[5.3, 75]
	ASA II	217	73177	72235	30	[26.2, 34.3]	16	7269	7198	22.2	[12.7, 36.1]	13	3743	3669	35.4	[18.9, 60.6]
	ASA III-IV	79	15368	14797	53.4	[42.3, 66.5]	6	1425	1372	43.7	[16, 95.2]	6	964	909	66	[24.2, 143.7]
Surgical indication	Missing	5	978	952	52.5	[17, 122.5]	0	156	153	0	[0, 241.3]	0	55	49	0	[0, 754.4]
	Osteoarthritis	297	98160	96929	30.6	[27.3, 34.3]	18	9761	9666	18.6	[11, 29.4]	19	5001	4910	38.7	[23.3, 60.4]
	Trauma	22	6718	6424	34.2	[21.5, 51.9]	5	689	662	75.6	[24.5, 176.3]	2	415	384	52.1	[6.3, 188.3]
	Other indication	26	7429	7257	35.8	[23.4, 52.5]	3	849	833	36	[7.4, 105.3]	2	501	488	41	[5, 148.1]
Surgical approach	Missing	3	667	656	45.8	[9.4, 133.7]	0	109	107	0	[0, 345.3]	0	22	22	0	[0, 1681.8]
	Posterolateral	250	69871	68737	36.4	[32, 41.2]	18	7675	7580	23.7	[14.1, 37.5]	16	3311	3234	49.5	[28.3, 80.3]
	Anterior	23	12948	12822	17.9	[11.4, 26.9]	2	288	287	69.7	[8.4, 251.8]	0	612	598	0	[0, 61.7]
	Anterolateral	74	29799	29348	25.2	[19.8, 31.7]	6	3383	3340	18	[6.6, 39.1]	7	2027	1977	35.4	[14.2, 73]
Fixation	Missing	1	469	460	21.7	[0.6, 121.1]	0	34	34	0	[0, 1099.9]	0	10	8	0	[0, 4543.1]
	Cemented	101	29191	28638	35.3	[28.7, 42.9]	18	5685	5606	32.1	[19, 50.7]	7	1293	1254	55.8	[22.5, 115.1]
	Hybrid	43	9829	9654	44.5	[32.2, 60]	1	1685	1665	6	[0.2, 33.5]	4	921	903	44.3	[12.1, 113.4]
	Uncemented	205	73796	72811	28.2	[24.4, 32.3]	7	4051	4008	17.5	[7, 36]	12	3748	3665	32.7	[16.9, 57.2]
Bearings surface	Missing	34	10459	10227	33.2	[23, 46.5]	0	603	590	0	[0, 62.6]	0	129	125	0	[0, 296.1]
	Ceramic on PE	181	56009	55231	32.8	[28.2, 37.9]	11	5943	5876	18.7	[9.3, 33.5]	11	1587	1557	70.6	[35.3, 126.4]
	Metal on PE	110	31121	30585	36	[29.6, 43.3]	14	2721	2683	52.2	[28.5, 87.5]	7	2809	2729	25.6	[10.3, 52.8]
	Ceramic on Ceramic	10	8231	8159	12.3	[5.9, 22.5]	1	2069	2046	4.9	[0.1, 27.2]	2	818	797	25.1	[3, 90.7]
	Zirconium on PE	14	6486	6395	21.9	[12, 36.7]					[,]	0	507	503	0	[0, 73.3]
	Metal on metal	1	979	966	10.4	[0.3, 57.7]	0	119	118	0	[0, 311.7]	3	122	119	251.6	[51.9, 735.3]

Appendix Table 3: Description of knee procedures by antibiotics regimen. * Revision rate for infection per 10,000 person-years

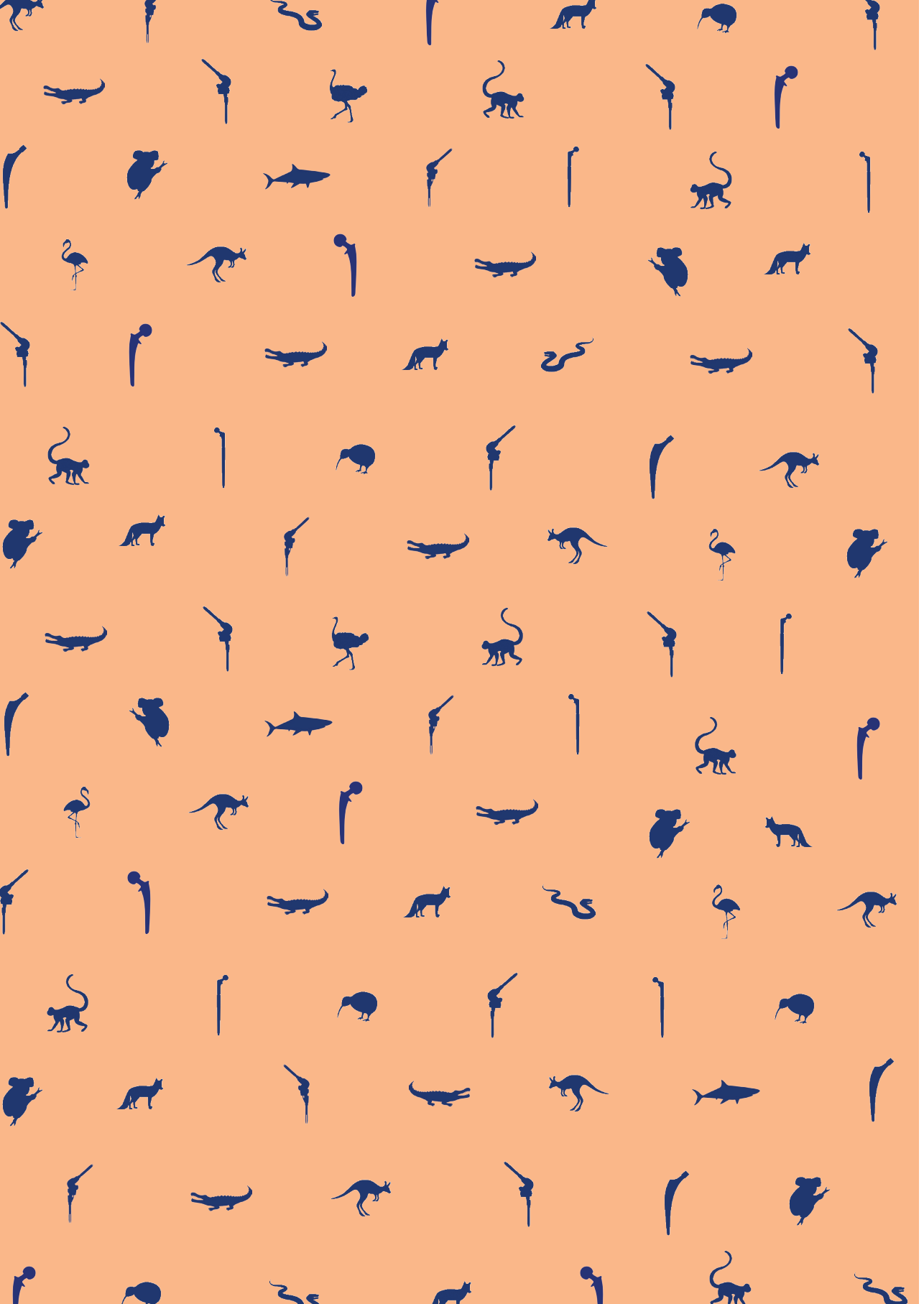
		Cefazolin multiple dose					Cefazolin single dose					Cefuroxime multiple dose				
		Revision	n	Person-years	Rate	95%CI	Revision	n	Person-years	Rate	95%CI	Revision	n	Person-years	Rate	95%CI
Overall		260	96791	96237	27	[23.8, 30.5]	24	9880	9826	24.4	[15.6, 36.3]	19	4796	4767	39.9	[24, 62.2]
Year of surgery	2011	19	16735	16652	11.4	[6.9, 17.8]	2	1785	1775	11.3	[1.4, 40.7]	2	927	924	21.7	[2.6, 78.2]
	2012	48	18740	18643	25.7	[19, 34.1]	1	1925	1915	5.2	[0.1, 29.1]	2	948	945	21.2	[2.6, 76.5]
	2013	55	19288	19162	28.7	[21.6, 37.4]	3	1911	1909	15.7	[3.2, 45.9]	1	977	970	10.3	[0.3, 57.4]
	2014	53	20920	20814	25.5	[19.1, 33.3]	6	2170	2154	27.9	[10.2, 60.6]	6	1018	1008	59.5	[21.8, 129.5]
	2015	85	21108	20966	40.5	[32.4, 50.1]	12	2089	2073	57.9	[29.9, 101.1]	8	926	920	87	[37.5, 171.3]
Sex	Male	143	33501	33244	43	[36.3, 50.7]	16	3317	3293	48.6	[27.8, 78.9]	7	1539	1532	45.7	[18.4, 94.1]
	Female	115	62932	62638	18.4	[15.2, 22]	8	6558	6528	12.3	[5.3, 24.1]	12	3250	3228	37.2	[19.2, 64.9]
	Missing	2	358	355	56.3	[6.8, 203.2]	0	5	5	0	[0, 7355.7]	0	7	7	0	[0, 5254.1]
Age	Missing	1	152	150	66.8	[1.7, 372]	0	4	4	0	[0, 9194.6]	0	7	7	0	[0, 5254.1]
	<60	47	17104	17038	27.6	[20.3, 36.7]	5	1726	1721	29.1	[9.4, 67.8]	6	769	761	78.8	[28.9, 171.6]
	60-65	55	19282	19216	28.6	[21.6, 37.3]	3	1951	1949	15.4	[3.2, 45]	6	948	942	63.7	[23.4, 138.7]
	66-70	53	19483	19414	27.3	[20.4, 35.7]	7	1905	1899	36.9	[14.8, 76]	2	983	980	20.4	[2.5, 73.7]
	71-75	43	17982	17892	24	[17.4, 32.4]	3	1893	1885	15.9	[3.3, 46.5]	2	938	938	21.3	[2.6, 77]
	76-80	37	13566	13455	27.5	[19.4, 37.9]	4	1367	1351	29.6	[8.1, 75.8]	1	664	661	15.1	[0.4, 84.3]
	>80	24	9222	9072	26.5	[17, 39.4]	2	1034	1017	19.7	[2.4, 71]	2	487	479	41.8	[5.1, 150.9]
BMI	Missing	97	48461	48194	20.1	[16.3, 24.6]	6	5458	5435	11	[4.1, 24]	4	2518	2508	16	[4.3, 40.8]
	<18.5	0	96	95	0	[0, 386.8]	1	15	15	673.8	[17.1, 3754.3]	0	2	2	0	[0, 18389.2]
	18.5-24.9	20	7664	7601	26.3	[16.1, 40.6]	1	727	720	13.9	[0.4, 77.4]	2	370	369	54.3	[6.6, 196]
	25-29.9	74	19919	19791	37.4	[29.4, 46.9]	8	1815	1801	44.4	[19.2, 87.5]	6	890	882	68	[25, 148.1]
	30-39.9	60	18701	18620	32.2	[24.6, 41.5]	7	1687	1679	41.7	[16.8, 85.9]	7	931	925	75.7	[30.4, 156]
	40+	9	1950	1935	46.5	[21.3, 88.3]	1	178	177	56.6	[1.4, 315.4]	0	85	83	0	[0, 446.4]

Appendix Table 3: Description of knee procedures by antibiotics regimen. * Revision rate for infection per 10,000 person-years (continued)

		Cefazolin multiple dose					Cefazolin single dose					Cefuroxime multiple dose				
		Revision	n	Person-years	Rate	95%CI	Revision	n	Person-years	Rate	95%CI	Revision	n	Person-years	Rate	95%CI
ASA	Missing	3	1350	1340	22.4	[4.6, 65.4]	0	314	314	0	[0, 117.6]	0	78	78	0	[0, 471.5]
	ASA I	41	16189	16138	25.4	[18.2, 34.5]	5	1509	1503	33.3	[10.8, 77.6]	4	636	633	63.2	[17.2, 161.9]
	ASA II	167	65977	65649	25.4	[21.7, 29.6]	13	6749	6722	19.3	[10.3, 33.1]	12	3276	3259	36.8	[19, 64.3]
	ASA III-IV	49	13275	13109	37.4	[27.7, 49.4]	6	1308	1288	46.6	[17.1, 101.4]	3	806	798	37.6	[7.8, 109.9]
Surgical indication	Osteoarthritis	234	92427	91909	25.5	[22.3, 28.9]	19	9232	9183	20.7	[12.5, 32.3]	19	4548	4521	42	[25.3, 65.6]
	Trauma	11	1495	1480	74.3	[37.1, 133]	0	135	135	0	[0, 273.2]	0	105	104	0	[0, 354.8]
	Rheumatic	7	1380	1369	51.1	[20.6, 105.3]	1	186	185	54	[1.4, 301]	0	65	65	0	[0, 566.5]
	Other indication	8	1489	1479	54.1	[23.4, 106.6]	4	327	323	123.8	[33.7, 317]	0	78	78	0	[0, 475.7]
Surgical approach	Missing	3	1241	1237	24.3	[5, 70.9]	0	89	89	0	[0, 413.3]	0	19	19	0	[0, 1935.7]
	Medial parapatellar	243	90617	90100	27	[23.7, 30.6]	21	9628	9578	21.9	[13.6, 33.5]	17	4169	4144	41	[23.9, 65.7]
	Mid/sub vastus	9	3715	3698	24.3	[11.1, 46.2]	1	90	89	112.4	[2.8, 626.2]	1	592	589	17	[0.4, 94.7]
	Other approach	5	1218	1203	41.6	[13.5, 97]	2	73	70	285.2	[34.5, 1030.2]	1	16	16	624.3	[15.8, 3478.6]
Fixation	Missing	1	882	880	11.4	[0.3, 63.3]	0	42	42	0	[0, 875.7]	0	20	20	0	[0, 1838.9]
	Cemented	247	86406	85905	28.8	[25.3, 32.6]	21	9202	9154	22.9	[14.2, 35.1]	19	4763	4735	40.1	[24.2, 62.7]
	Hybrid	3	5145	5113	5.9	[1.2, 17.1]	0	16	16	0	[0, 2351.3]	0	1	0	0	[0, 13000000]
	Uncemented	9	4358	4338	20.7	[9.5, 39.4]	3	620	615	48.8	[10.1, 142.6]	0	12	12	0	[0, 3064.9]

SECTION

2



CHAPTER

4

Hip and Knee Section, Treatment, Algorithm: Proceedings of International Consensus on Orthopaedic Infections

(J Arthroplasty. 2019 Feb;34(2S):S393-S397.)

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QUESTION 1:

Should early postoperative infection and acute hematogenous infection be treated and managed differently?

Recommendation:

There is no evidence to support the notion that early postoperative infection and acute hematogenous infection should be treated differently as long as the onset of symptoms is < 4 weeks (favourable <7 days). Implants are well-fixed, no sinus tract exists, and the isolated infecting organism is sensitive to an antimicrobial agent.

Level of Evidence: Moderate
Delegate Vote: Agree: 94%, Disagree: 5%, Abstain: 1% (Super Majority, Strong Consensus)

Rationale:

Early postoperative infection is usually defined as infection occurring within 3 weeks of index arthroplasty, although some authorities state that any infection within 3 months (90 days) of the index arthroplasty should be considered acute.[1] Hematogenous infections associated with a remote source are often classified as late infections, which can occur 1 to 2 years after arthroplasty.[2] Acute hematogenous infection is defined as infections with no more than 3 weeks of symptoms.[3] According to the Clinical Practice Guidelines by the Infectious Diseases Society of America, patients who have a well-fixed, functioning prosthesis without a sinus tract, infection occurring within 30 days of index arthroplasty or <3 weeks of onset of infectious symptoms, and having an organism susceptible to oral antimicrobial agents, should be candidates for debridement and implant retention (DAIR).[4] The International Consensus Meeting 2013 also proposed that DAIR should be considered in patients with infection occurring within 3 months of the index arthroplasty, with less than 3 weeks of symptoms in early postoperative infections, and those with symptoms less than 3 weeks in late hematogenous infection.[3] When these criteria are met, DAIR is a reasonable option for early postoperative or acute hematogenous infection. However, because of the relatively high failure rate of DAIR in some reports and the fact that mature biofilm on an implant surface forms within a few days, some studies have suggested that the DAIR should be restricted to patients with less than 5 days of infection symptoms.[5]

One prospective study demonstrated that 52% of acute hematogenous infections failed at 2-year follow-up following DAIR.[6] Treatment failure rates were 57.8% in

staphylococcal infection, 14.3% in streptococcal infections, and no failures were seen in gram-negative periprosthetic joint infection (PJI).[6] A second comparative study reported that the success rates after DAIR in hip and knee PJI may be significantly increased if treatment was initiated within 2 days of symptoms.[7] In the latter study, DAIR showed overall success rate of 82.1% for early infections and 57.1% for acute hematogenous infections. Patients with acute hematogenous infections had an 8-fold higher chance of failure. Given the higher failure rate in the acute hematogenous group, the authors suggested that treatment parameters for these infections required additional studies with higher patient numbers.[7] A recent study evaluating the outcome of DAIR showed no statistically significantly different treatment outcomes between early postoperative infection (15%) versus acute hematogenous infection (21%).[8] Modular components were exchanged in only 70% of the included patients in the latter study. Systemic host grade A (McPherson classification) was a strong predictor of treatment success.[8]

Several systematic reviews suggest that interventions in both early postoperative and acute hematogenous infections should be timely and aggressive (with exchange of modular parts), as each additional day of waiting lowers the odds for a successful outcome.[9-12] A recent meta-analysis reported the significant determinants of successful outcome following DAIR.[12] Time from onset of symptoms or index arthroplasty (<7 days) and the exchange of modular components were the most significant factors influencing outcome. In the latter meta-analysis, the authors detected that the reported success of DAIR has increased since 2004.[12] The exact reason for this improvement in outcome is not known but may relate to a publication in 2004 by Zimmerli et al which established an algorithm for DAIR.[10] The algorithm may have encouraged the orthopaedic community to change their indications for DAIR, attempt to optimize patients before DAIR by modifying risk factors for failure, and possibly altering the administration of antimicrobial regimen. Virulent organisms causing PJI are also predictors for treatment failure following DAIR, according to some studies. Staphylococcus aureus and methicillin-resistant S. aureus have been reported to result in a higher failure rate following DAIR when compared with gram-negative pathogens.[9,13] In addition, infections with methicillin-resistant Staphylococcus epidermidis and Vancomycin-resistant enterococci have been associated with inferior outcome following DAIR.[9,10] In contrast, in a study on early postoperative and acute hematogenous infections caused by S. aureus, this difference could not be shown.[14]

Acute hematogenous infection might be a marker of poor general health as almost half of the patients in one study had some critical medical comorbidity that may

have predisposed them to developing infection in the first instance.[15] Relatively high mortality rates around 20% after 2 years have been reported for patients with acute hematogenous infections, which could be attributed to higher rates of systemic sepsis at presentation in this patient population.[14,15]

In conclusion, DAIR is a viable option and a reasonable first therapeutic approach for patients with early postoperative and acute hematogenous infections. However, some studies have reported a high failure rate of this surgical treatment and a relatively high early mortality rates after DAIR for acute hematogenous infections compared with acute postoperative infections. These differences might be related to differences in the patho-etiology of these infections and the influence of the intrinsic host factors on the outcome. Therefore, studies focusing on improving treatment outcomes after acute hematogenous infections are desperately needed.

QUESTION 2:

Should operative treatment differ in patients with systemic sepsis in the setting of PJI?

Recommendation:

Yes. Patients with systemic sepsis in the setting of PJI should have surgical bioburden reduction, either with implant retention or resection of components (if indicated and safe), along with concurrent antimicrobial therapy. Reimplantation should be delayed until sepsis is resolved.

Level of Evidence:	Limited
Delegate Vote:	Agree: 79%, Disagree: 19%, Abstain: 2% (Super Majority, Strong Consensus)

Rationale:

Infection of total joint arthroplasty is a known and devastating complication all surgeons seek to avoid. Despite best efforts, prosthetic joints can be seeded from local and systemic sources.[16-24] Although periprosthetic joint infection (PJI) usually presents without systemic signs of pyrexia, chills, and other symptoms, occasional PJI may result in systemic sepsis when the blood culture may also be positive for infection. In the context of systemic sepsis, hematogenous spread is the definitive mechanism by which PJI develops in previously well patients. Orthopaedic infections appear to be caused by the same common group of bacterial pathogens. In this group, the majority are gram-

positive cocci, namely, Staphylococcus aureus and Staphylococcus epidermidis. There is the ever present threat of methicillin-resistant S. aureus as a difficult PJI infection to remove. Moreover, the growing number of vancomycin-resistant enterococcus and other serious Gram-negative bacteria are also a concern. Gram-negative bacteria are associated with more severe episodes of sepsis because of the production and release of lipopolysaccharides (endotoxin).

Highlighted across several studies is the concept of the arthroplasty surface acting as a unique microbial substratum.[25] Gallo et al reported the affinity of S epidermidis to attach to the polyethylene surfaces as opposed to S. aureus preference for bare metal. In each of the papers examined by Gallo et al, the presence of biofilm on the wearing or corroded surfaces of the implants was a key factor in the bacterial resistance to host and antimicrobial attack. A paper referenced in the Gallo et al review by Gristina, characterized the colonization of the prosthesis as a "race for the surface".[25,26] This concept is apt at highlighting the need for pathogens to colonize, undeterred by local and host factors.

These concepts are of pivotal importance when examining the published material reviewed here in the context of the original question "To evaluate whether operative treatment should differ in patients with systemic sepsis in the setting of prosthetic joint infection." As demonstrated in this review and supported by the significant cohort size, PJI can occur as a consequence of local or hematogenous colonization. Overall, severity of infection is higher with hematogenous spread, as is the difficulty in clearing the infection for subsequent implant revision.[27-29] Osteomyelitis before implantation of prosthetic joints indicates increased risk as reported by Jerry et al.[19] The nearly 5-fold increase in recurrence rates seen in patients with prior bone infection serves as a significant warning to surgeons to adequately debride as much contaminated surface as is feasible to allow for control of infection and subsequent implantation.[19]

Based on the articles included in this review, there is no evidence to suggest that the implantation of prosthetic joints during an episode of sepsis is advisable. Often, however, joint arthroplasty procedures will need to be performed to alleviate the tremendous pain associated with infective destruction of a joint surface. Each of the included studies recommended a staged approach to surgical management of PJI with the most common approach being 2-staged revision. There is very limited evidence to support retention of implants if a curative outcome is the main objective of the treatment. Also, there is a lack of evidence to suggest initiating antibiotic therapy to counter the systemic sepsis before the first stage revision surgery. Although

identification and eradication of clinically obvious secondary foci, similar to indwelling catheters and skin, soft tissue, respiratory, and genitourinary infections could be of vital importance for controlling the PJIs and preventing subsequent relapse. Therefore, similar to PJIs without systemic sepsis, a combination of effective debridement and concurrent intravenous antimicrobial therapy is the current best practice standard of care. The main limitation associated with the effective execution of this thorough and proven care strategy seems to be the accurate diagnosis of the complete clearance of infection to restore aseptic status to the patient.

It must be noted that, as of the completion of this review, there are no studies that directly evaluate whether operative treatment should differ in patients with systemic sepsis in the setting of prosthetic joint infection. There are a number of closely related papers quoted previously, but that is the limit of current knowledge. It is, however, our opinion that patients with systemic sepsis exhibiting constitutional symptoms are at serious risk and should be treated urgently. The best option of treatment is bioburden reduction which involves extensive soft tissue debridement and removal of infected prostheses.

QUESTION 3:

What should be done for patients with persistent wound drainage after total joint arthroplasty? What are the indications for surgical intervention?

Recommendation:

Management of draining wounds after total hip or knee arthroplasty consists of 2 main steps; nonoperative and operative. The nonoperative measures include modification of venous thromboembolism prophylaxis, nutritional supplementation, dressing measures (such as negative-pressure wound therapy), and restriction of range of motion. If draining continues for more than 7 days after implementing the nonoperative measures, operative interventions may be indicated including irrigation and debridement, synovectomy, and single-stage exchange. In certain situations, superficial wound washout may be indicated (Fig. 1).

Level of Evidence:	Limited
Delegate Vote:	Agree: 89%, Disagree: 8%, Abstain: 3% (Super Majority, Strong Consensus)

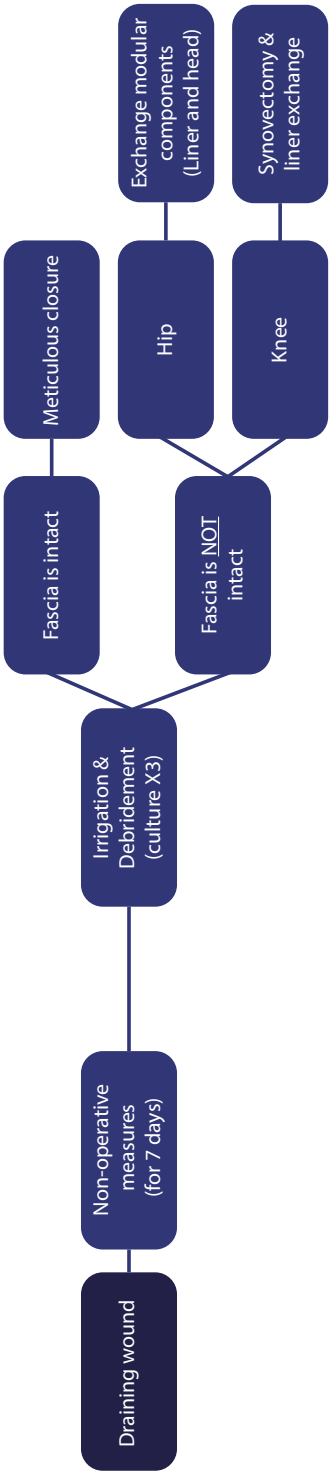

Figure 1: Management of draining wounds after total joint arthroplasty.

Rationale:

Drainage after total hip and knee arthroplasty increases the risk of subsequent superficial or deep infection. Studies have shown that the risk of deep infection increases by 29% after total knee arthroplasty (TKA) and 42% after total hip arthroplasty (THA) with each additional day of drainage.[30]

DEFINITION

Persistent wound drainage (PWD) by definition is an area of drainage greater than 2x2 cm on the incisional gauze that persists over 72 hours postoperatively.[31] Drainage can be due to hematoma, seroma, fat necrosis, or defects in arthrotomy closure.[32]

Nonoperative Measures

Ceasing Anticoagulation Agents Anticoagulation agents for venous thromboembolism prophylaxis have been shown to affect PWD after total hip and knee arthroplasty. Low-molecular-weight heparin leads to higher rates of prolonged wound drainage after THA and TKA compared with aspirin and warfarin.[30] Fondaparinux had fewer wound complications but no difference in infection after TKA compared with aspirin, low-molecular-weight heparin or warfarin.[33] Dabigatran was found to have an increased rate of wound drainage and increased length of stay after TKA and THA.[34] Therefore, one of the first steps in patients with PWD is to cease the anticoagulation medications, if possible.

Negative-Pressure Wound Therapy

Negative-pressure wound therapy (NPWT) applied to closed incisions after TKA or THA has been shown to reduce the rate of superficial wound infection.[35] In patients undergoing primary total hip or knee arthroplasty, NPWT has been shown to reduce postsurgical wound exudate, number of dressing changes, a trend toward reduced length of stay, and a trend toward reduced postop surgical wound complications.[36] Using ultrasound to measure volume, NPWT has been shown to reduce the size of postop seromas when compared to a standard dressing.[37] NPWT applied 3-4 days after THA for persistent drainage resulted in drainage resolution in 76% while 24% required further surgery.[38] As part of local wound care in the first 7 days of PWD, we recommend using incisional NPWT systems.

Nutrition

Malnourishment has several definitions. One of the most commonly used ones is serum transferrin <200 mg/dL, serum albumin <3.5 g/dL, or total lymphocyte count <1500/

mm3. Poor nutritional status is associated with a significant (up to 5-fold) increase in risk of wound complications after THA and TKA.[39-41] Malnourished patients are more likely to fail nonoperative treatment (odds ratio 18.29), as well as surgical debridement (35% vs 5%, P < .0003).[3] We strongly urge modifying the nutritional status of the patients before an elective arthroplasty procedure. In case of a PWD, postoperative nutritional supplements can help improving the wound healing process.

Surgical Intervention

Surgical intervention for drainage should be considered after 5-7 days of PWD.[30-32] Saleh et al conducted a 20-year surveillance study and concluded that patients with longer 5 days of drainage have 12.7 times higher likelihood to develop surgical site infection in comparison with those who had less drainage time.[31] Therefore, we recommend proceeding with surgical intervention if the PWD continues for more than 7 days.

The first step of the surgical intervention is irrigation and debridement (I&D) and obtaining at least 3 intraoperative cultures. Irrigation is recommended to be performed with at least 9 L of an irrigation solution, such as normal saline or an aqueous iodophor solution. At this point, if the fascia is found to be intact we recommend meticulous closure. However, if the fascia is not intact, modular components should be exchanged.[30,32] Studies have shown promising results with single I&D. Jaberi et al reported that in THA and TKA patients with PWD, drainage stopped in 76% of patients after single-stage I&D.[30] The remaining 24% required subsequent treatments such as repeat I&D, removal of implant, or long-term antibiotic administration.

QUESTION 4:

How should infected bilateral hip or knee arthroplasties be managed?

Recommendation:

The optimal surgical treatment for infected bilateral hip or knee arthroplasties is unknown. While revising the components likely provides improved outcomes over limited debridement with component retention, data do not preferentially support either a single-stage or 2-stage exchange revision arthroplasty.

Level of Evidence:	Limited
Delegate Vote:	Agree: 83%, Disagree: 11%, Abstain: 6% (Super Majority, Strong Consensus)

Rationale:

Infected bilateral hip or knee arthroplasties presents a rare treatment dilemma for both the patient and surgeon. The literature on this topic is limited, however, with only 2 small case series and at least 9 case reports describing multiple simultaneous periprosthetic joint infections.[16,20,42-56] Treatment options include debridement with component retention, single-stage revision, and two-stage revision surgery. The largest study by Wolff et al on infected bilateral total knee arthroplasty demonstrated improved outcomes with a simultaneous 2-staged revision when compared with irrigation, debridement, and prosthetic salvage.[45] Concerns exist about the morbidity of a 2-stage revision and the immobility and restricted weight bearing on both extremities during the antibiotic spacer period. A series of 16 bilateral infected arthroplasty patients by Zeller et al noted good results with single-stage exchange and another center reported 2 cases of successful treatment of bilateral infected total hip arthroplasty with a simultaneous single-stage revision.[46,56]

Surgical treatment of bilateral infected arthroplasties should consider factors such as the virulence of the organism, medical comorbidities, patient age, and functional status. For bilateral acute hematogenous infection, some authors performed an irrigation, debridement, and exchange of modular bearing surfaces followed by targeted antibiotic therapy, but these results were limited to case reports.[44,47-52,54,55] For chronic bilateral periprosthetic infections, these case reports described the same therapeutic management as is commonly favoured for unilateral infection: 2-stage revision with placement of an antibiotic impregnated cement spacer for a period of at least 6-8 weeks before reimplantation.[48,53,54] An interval of several days occurred between each side undergoing surgery in these series, while others performed simultaneous bilateral revision surgery. The decision whether to perform simultaneous bilateral revision surgery for periprosthetic joint infection should also consider the patient's medical comorbidities and functional status. With only small retrospective case series in the literature, we can issue a limited recommendation that revising the components likely results in improved outcomes; however, we do not have the data to recommend a single-stage or 2-stage revision procedure over the other.

We do however feel that performing resection arthroplasty of 2 joints under the same anaesthesia represents immense physiological insult to the patient and all efforts should be made to minimize the operative time and blood loss in these patients, if bilateral surgery is contemplated. The use of two expert teams to operate at the same time has been suggested by some investigators.

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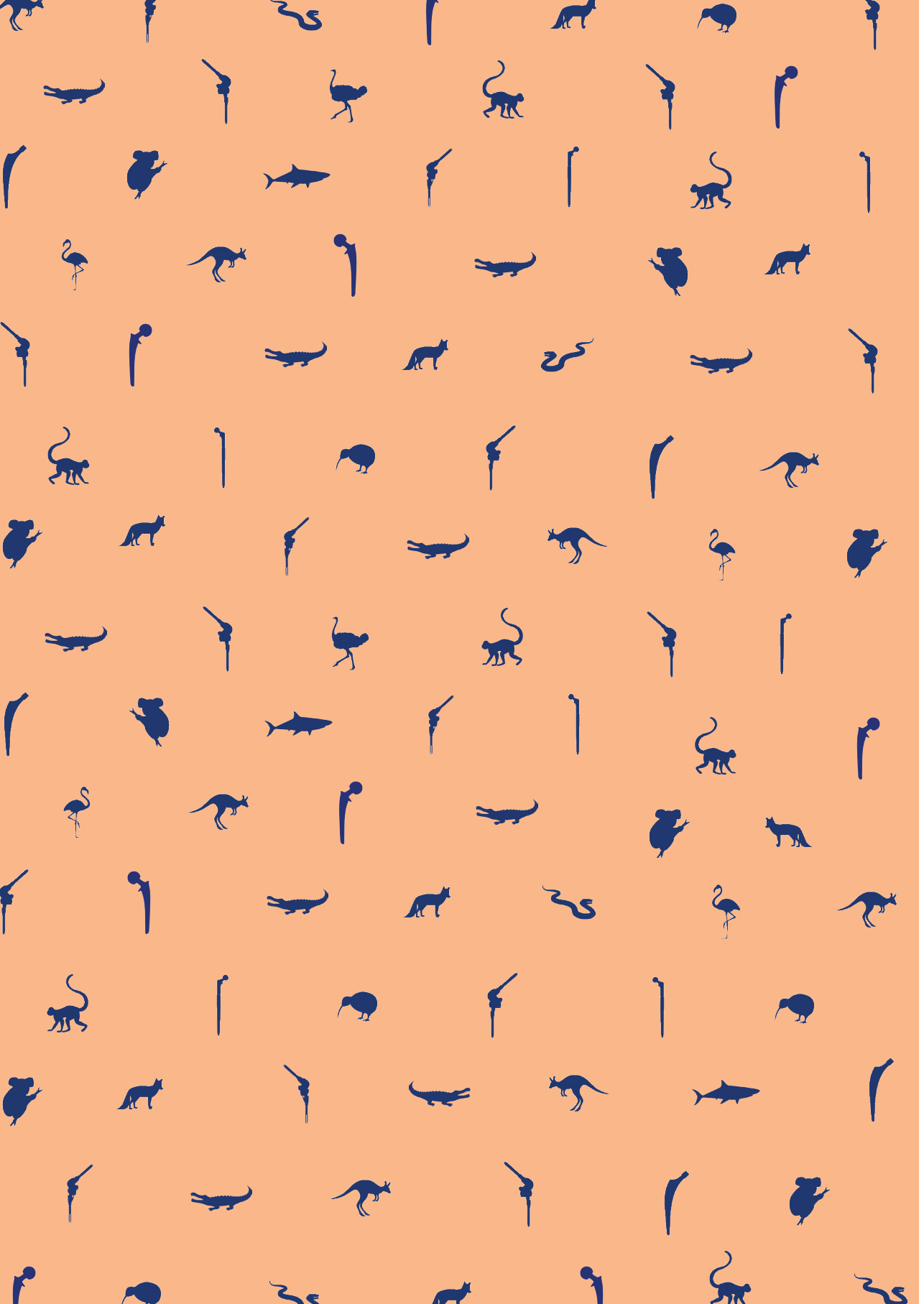

CHAPTER

5

Hip and Knee Section, Treatment, Two-Stage Exchange:

Proceedings of International Consensus on Orthopaedic Infections

(J Arthroplasty. 2019 Feb;34(2S):S439-S443.)

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QUESTION 1:

What is the optimal timing for reimplantation of a 2-stage exchange arthroplasty of the hip and knee?

Recommendation:

The optimal timing for reimplantation of a 2-stage exchange arthroplasty of the hip or knee has not been established. Reimplantation may be performed when the treating medical team feels that the infection is under control.

Level of Evidence: Moderate
Delegate Vote: Agree: 93%, Disagree: 4%, Abstain: 3% (Super Majority, Strong Consensus)

Rationale:

There is no conclusive evidence for defining the optimal timing between resection arthroplasty and reimplantation in a 2-stage revision arthroplasty for periprosthetic joint infections (PJIs). Multiple studies have reported time to reimplantation ranging from a few weeks to several months or even years.[1-11] Literature has used various definitions for PJI 2-stage treatment success or failure as well as different variables influencing the timing of reimplantation. Due to this heterogeneity, they have failed to answer this question. Success of treatment with a 2-stage arthroplasty varies between <70% and 100%, with no direct correlation to the spacer time interval.[1,2,6,7,9,11]

Several studies have reported on time to reimplantation and its influence on success or failure. Haddad et al reported no increase in reinfection rates by reducing the interval to 3 weeks.[5] Sabry et al found that an increased duration between resection and reimplantation was associated with higher rates of infection recurrence in a cohort of 314 infected TKAs treated with 2-stage exchange arthroplasty.[7] Their median interval between stages was 103 days (range, 2-470 days). A study by Kubista et al also found that a longer time period between spacer insertion and reimplantation was associated with increased PJI recurrence.[8] In contrast, Babis et al obtained a 100% success rate when using a long interval - mean 9 months (range, 8-12 months) in a group of patients with a high percentage of multi-resistant bacteria.[9]

One common belief is that a delayed second stage or reimplantation will result in higher rate of treatment success. However, this is not based on strong evidence and may lead to an unnecessary long inter-stage interval with its associated morbidity.

Aali-Rezaie et al, in a recent, large retrospective cohort study evaluating patients with 2-stage exchange arthroplasty, did not detect a clear association between time to reimplantation and treatment failure.[10] Furthermore, they found that delaying the time to reimplantation did not significantly improve treatment success of 2-stage exchange arthroplasty. In addition, Vielgut et al found, in a study of 76 hip infections, that patients who had their reimplantation between 4 and 11 weeks had a significantly higher success rate when compared to less than 4 and greater than 11 weeks.[6]

When deciding on the optimal timing for reimplantation, most surgeons prefer to rely on a combination of clinical evaluations, such as a completely healed wound, no pain, and serologic tests trending downward after a period of antibiotic therapy.[11] Various studies recommend a complete work up with normalized laboratory and clinical variables to assure infection control before reimplantation.

QUESTION 2:

Is it safe to retain a stable cement mantle, for later use, in patients undergoing resection arthroplasty for periprosthetic joint infections (PJIs)?

Recommendation:

Meticulous debridement and removal of all foreign material, including cement, should be part of resection arthroplasty in the management of periprosthetic joint infections (PJIs). Limited data suggest that under strict conditions and following a meticulous surgical technique, a stable cement mantle in the femur may be left in place for later use in order to minimize damage to the femoral bone stock.

Level of Evidence:	Limited
Delegate Vote:	Agree: 63%, Disagree: 29%, Abstain: 8% (Super Majority, Weak Consensus)

Rationale:

Historically, resection arthroplasty for periprosthetic joint infections (PJIs) involved removal of all the foreign material including cement, as these materials can act as a nidus for the biofilm and persistence of infection.[12-16] However, removal of the cement mantle increases operative time and causes increased morbidity through bone loss and fractures. The in-cement revision technique is a useful, well-described technique used

in aseptic conditions to avoid the tedious task of cement removal and therefore avoid complications associated with cement extraction.[17-21] Retention of an intact cement mantle in cases of resection arthroplasty for PJI would be preferable to avoid the morbidity associated with its removal and would make subsequent reimplantation technically easier.

The concern for retaining cement in the setting of PJI has been supported by in vitro studies. Kendall et al examined microbial growth of staphylococcal species on the surface of antibiotic-loaded cement discs incubated in broth. While the broth itself was sterilized by the discs after 96 hours, growth was consistently seen on the surface of the cement discs themselves. The cement, therefore, seemed to be a habitable surface for continued growth of bacteria, despite elution of antibiotics.[22] Mariconda et al demonstrated that fluid around antibiotic-loaded cement that is sonicated can yield positive cultures, even if aspiration fluid was culture-negative, indicating that biofilms can persist on antibiotic-loaded cement.[23] Tunney et al and Minelli et al showed that the biofilm could form even on antibiotic-loaded cement, depending on the inoculum and the type and dosing of the antibiotic agent.[24,25] Although Griffin et al could not demonstrate biofilm formation in explanted spacers, Ma et al demonstrated that 30.7% of spacers had bacterial contamination at the time of the second stage.[26,27] This laboratory data should give some cause for concern for the retention of cement in the setting of infection, even if loaded with antibiotics.

The clinical data on this topic are extremely limited. There are 2 case series that examine this specific issue, both involving a stable cement mantle in revision total hip arthroplasty for infection. Morley et al reviewed 15 total hips with 2-stage revisions for PJIs while retaining the original cement mantle, and reported infection-free outcomes in 14 of 15 patients.[28] The authors used very strict selection criteria for the patient cohort including a stable cement mantle, prior use of antibiotic loaded cement, and meticulous burring of the cement mantle to remove the biofilm and liberate antibiotics as vital to the success of this technique. In a similar study, however, Leijtens et al reported success in only two of 10 patients undergoing 2-stage revision total hip arthroplasty for infection at an average of 26 months.[29] It should be noted that this study did not mention whether the existing cement mantle contained antibiotics or not.

There is only one level IV study showing good results with a retained stable cement mantle for later use in resection arthroplasty in the treatment of PJIs. Although this technique presents theoretical advantages, there is a lack of robust evidence in the

literature to support its routine use. Direction for further research might include the use of chemical debridement agents, such as dilute povidone-iodine, chlorhexidine irrigation, and/or acetic acid preparations, which some evidence suggests might help eradicating microbes and biofilms in some settings.[30] The role of chemical debridement agents in eliminating sessile bacteria and biofilms on the surface of retained cement has yet to be explored. With further research, the answer to this question might become known.

QUESTION 3:

Should surgeons make an effort to remove cement that has extruded into the pelvis or at difficult anatomical positions in patients with periprosthetic joint infections (PJIs)?

Recommendation:

The orthopaedic surgeon should carefully consider whether the potential benefits of cement extraction from the pelvis or difficult anatomical positions outweigh the potential risks of persistence of infection.

Level of Evidence:	Consensus
Delegate Vote:	Agree: 85%, Disagree: 9%, Abstain: 6% (Super Majority, Strong Consensus)

Rationale:

Extrusion of cement during primary arthroplasty is reported to occur in 25% of patients.[31] Bacteria can form a biofilm on foreign bodies in patients with prosthetic joint infections.[32] Therefore, in patients with periprosthetic joint infections (PJIs), who are undergoing resection arthroplasty, it is recommended that the prosthesis and all foreign material including bone cement be removed and thorough debridement performed. Whether or not cement in the pelvis or in difficult anatomic positions contributes to the risk of persistent infection after revision arthroplasty has not been studied.

When cement is extruded into the pelvis or difficult anatomic positions during primary arthroplasty, there is a risk of neurological (obturator nerve palsy, femoral or sciatic nerve involvement), urological (such as a foreign body in the bladder wall), or vascular (with compression of the external iliac vein) complications.[33-38] During extraction of

extruded cement, the risk of these complications may be even greater due to the manipulation needed for extraction.

It is common wisdom and belief among surgeons that foreign material in an infected joint may harbor the biofilm formed by the infecting organism. Leaving behind foreign material during resection arthroplasty and debridement, thus, runs the theoretical risk of allowing for the biofilm and infection to persist and could therefore potentially jeopardize the success of surgical debridement. The latter dogma has actually never been proven in a conclusive study. It is also known that removal of foreign material, such as cement, from anatomically sensitive and/or inaccessible areas may require a wider surgical approach (such as laparotomy for extruded cement into the pelvis) or manipulation of structures such as organs (e.g., bladder, bowel), vessels (e.g., vena cava or major veins), or nerves (e.g., sciatic or plexus). The manipulation of these structures may threaten the life of the patient and/or lead to catastrophic complications. Thus, we believe surgeons should exercise their wisdom when dealing with patients with PJIs and extruded cement or other foreign materials in anatomically sensitive and/or inaccessible areas.

QUESTION 4:

Does the use of non-antibiotic impregnated allograft for bone defects during reimplantation increase the risk of recurrence of SSIs/PJIs?

Recommendation:

There is no evidence to demonstrate that using non-antibiotic impregnated allograft for management of bone defects during reimplantation (following PJIs) increases the risk of recurrence of SSIs/PJIs.

Level of Evidence:	Limited
Delegate Vote:	Agree: 88%, Disagree: 9%, Abstain: 3% (Super Majority, Strong Consensus)

Rationale:

Systematic reviews were undertaken using PubMed, Cochrane Library, SCOPUS, and Google Scholars databases and relevant papers were reviewed. During review, it became evident that there is a dearth of information directly assessing treatment of periprosthetic joint infections (PJIs) when a non-antibiotic impregnated allograft was

used. Overall, 51 articles were reviewed in full. The evidence is summarized in the following paragraphs.

Following the increased popularity of the use of allograft bone in tumor surgery in 1970s, infection has become a major concern.[39] The early reports of infection rates range from 13.2% by Mankin et al to 11.7% by Lord et al and were followed by 7.9% in a comprehensive report by Mankin et al in 2005.[40-42] All authors believed that higher rates of infection could be attributed to the disease nature, extent, duration, and complexity of the procedures and not related to the allograft itself.[40-42]

Tomford et al in a retrospective study reviewed 324 patients who received allografts and showed a negligible clinical incidence of infection.[43] The incidence related to the use of large allografts was approximately 5% in bone tumor and 4% in revision of a hip arthroplasty. These rates of infection were not substantially different from those that have been reported in similar series in which sterilized prosthetic devices were used.[44] One of the early reports of allografts in revision total hip arthroplasty (THA) was published by Berry et al.[44] They used bone allografts in 18 patients during 2-stage revision of septic THA failures. At a mean of 4.2 years after reimplantation, only 2 patients had a recurrence of the infection (11%).

Several retrospective cohort studies have evaluated the use of allograft bone during total hip reimplantation surgery, the second stage of planned 2-stage exchange arthroplasty for infection. The majority of these studies have demonstrated recurrent infection rates of 0 to 9% in cohorts consisting of 11-27 patients with midterm to long-term follow-up.[5,44-49] Two studies reported less favourable reinfection rates of 11% (18 patients, mean 4.2 year follow-up) and 14% (57 patients, mean 9 year follow-up) .[50,51]

Traore et al reported a higher rate of 20% for reinfection at mean 3 years.[50] Loty et al reported a cohort of 90 cases with 8 (9%) reinfections over an unknown follow-up period in 1-stage hip revision for infection.[51] Lange et al performed a systematic review on using bulk allograft for second-stage reimplantation of hip arthroplasty and revealed a reinfection rate of four of 43 (9.3%) at an average follow-up of 6 years.[52] This was comparable to the reinfection rate reported for 2-stage revision without using allograft. Alexeeff et al also had no recurrence of infection in 11 septic failures of THA that underwent 2-stage revision THA using massive structural allografts and were followed for an average of 47.8 months.[48]

Tsahakis et al reported on 15 cases that used allograft for revision knee surgery, and of the three infected knees in their case series, there was no recurrence of infection.[53] Wilde et al performed a retrospective review of 16 revisions TKAs with allograft.[54] There were two infected cases and neither of these experienced reinfection. Stockley et al reviewed 32 deep-frozen irradiated allografts used for the reconstruction of bone defects in 20 knees with an average follow-up of 4.2 years.[55] Three knees developed infection (9.3%), and one of these was a revision for infection. However, they did not believe that the allograft was the source of sepsis.

Further reports by Harris et al (14 patients including 2 infected cases), Mow et al (15 structural allografts), and Engh et al (35 allografts), examined revision TKA cases and found no cases of reinfection.[56-58] Ghazavi et al reported 3 infections (7%) using bulk allograft in 38 patients including 3 infections that underwent revision. Two of the 3 cases who had previous infections experienced reinfection.[59] In a report by Clatworthy et al on 52 cases, there were 6 infections, all of which underwent revision TKA with a bulk allograft. One of the 6 patients who had a previous infection developed recurrence of infection.[60]

English et al reported their results of using impaction allografting in the second-stage reimplantation of 53 infected hip arthroplasties.[61] After a mean follow-up of 53 months, 4 patients had recurrence of infection (7.5%). In reports by Dennis et al (32 allografts) and Garino et al (8 cases of impaction allografts), there were no infections at final follow-up.[62,63]

Hockman et al reviewed 65 consecutive revision TKAs including 12 infections at a minimum 5-year follow-up.[64] Three of the 12 (25%) previously infected cases developed infections. They concluded that knees originally revised for infection were more likely to fail. Bush et al reviewed options for reconstructing massive bone loss and recommended against using allograft in some situations including chronic infections.[65] Backstein et al reported 68 cases of massive allografts for revision TKA, and 11 of these were septic revisions.[66] They found 4 infections (6.5%). The authors did not include how many of them had surgery for septic revisions. They believed that because of the large size of the used allograft bone and the number of previous surgeries the patients had, the infection rate was modest.

Lotke et al reported on 48 cases including one infection that received impaction allografting in revision TKA.[67] At an average follow-up of 3.8 years, they had 2 infections

(5%). Bezwada et al reviewed 11 knees in 10 patients who underwent revision with distal femoral allografts and stemmed components.[68] After a mean follow-up of 42 months, they had no infections. They recommended against the use of plate fixation to decrease extensive soft tissue dissection and the risk of infection.

Engh et al reported no cases of reinfection in 49 revision knees with severe tibial bone defects, 5 of which were revisions for infection.[69] Rudelli et al reported on 32 loose and infected total hip arthroplasties that underwent revision with a bone graft in a 1-stage procedure.[70] After a mean follow-up of 103 months, infection recurred in 2 (6.2%) cases.

Burnett et al reported on 28 knees that underwent revision TKA with an allograft at a follow-up of 48 months.[71] Only 1 patient (3.5%), who received cancellous graft for a contained defect, developed an infection. They did not mention if this was an infected revision. Lyall et al investigated 15 revision TKA patients, including 3 revisions for infections with severe tibial bone loss.[72] These patients were followed for a mean of 5.4 years, and they found 1 (6%) recurrence of infection at 3.5 years.

Bauman et al retrospectively reviewed 74 patients (79 knees) who had revision TKAs with structural allografts.[73] Of this cohort, 65 patients (70 knees) were followed for a minimum of 5 years or until revision or death. Five of 16 failures were secondary to infection (7.1%). Two of these patients had a history of infection and 2 had local wound problems at the time of revision surgery requiring muscle flap or skin grafting. The authors concluded that the large bulk allografts were more likely to fail secondary to infection or non-union.

In an overview on management of bone loss in revision TKR, Lombardi et al did not mention infection as a disadvantage (i.e., late resorption, fracture, non-union, or risk of disease transmission) of using an allograft.[74] Lee et al retrospectively reviewed 27 patients who underwent 2-stage revision arthroplasty using structural allografts to treat massive bone defects in infected hip arthroplasty.[49] After a mean follow-up of 8.2 years, only 1 patient (3.7%) experienced a reinfection.

Richards et al reported on a cohort of 24 patients reconstructed with femoral head allografts at the time of revision TKA and they compared them to 48 cases without allograft. All reported quality of life scores were higher in the allograft group.[75] They did not observe any failures. Wang et al reported 28 patients with femoral head allografts for revision TKA at a mean follow-up of 76 months.[76] They had no complications and no

infections. Vasso et al reviewed multiple papers on options for management of bone loss in revision TKA.[77] They concluded that modular metal and tantalum augmentation may considerably shorten operative times with a potential decrease in the incidence of complications including infection associated with the use of allografts. In a review of 27 patients who had undergone revision TKA using a fresh frozen femoral head allograft and followed for 107 months, there was 1 (3.7%) recurrence of infection.[78]

Recently, Beckmann et al performed a systematic review on the treatment of revision TKA with bony structural allografts (overall including 476 cases) and porous metal cones (overall including 223 cases).[79] They compared the failure rates using a regression model with adjustment for discrepancies in follow-up time and number of grafts used (femoral, tibial, or both). They did not separate septic revisions from aseptic revisions, but there was little difference in the infection rates between allograft and porous metal groups.

Mancuso et al also reviewed the available English literature since 2007 on options for reconstruction of bone defects in revision TKA.[80] Infection was reported in eight of 271 (3%) allografts, 43 of 662 (6%) metal cones, and 27 of 901 (3%) sleeves, indicating that the use of allografts did not lead to a higher rate of infection than metal cones or sleeves.

Sandiford et al compared femoral head structural allografts and trabecular metal cones for the management of severe bone defects during revision TKA.[81] They evaluated 30 allografts and 15 metal cones at a mean follow-up of 9 years and found no differences in pain, function, or repeat revision. The reason for revision was infection in 2 patients. They observed no reinfection in either group, although 1 patient in the allograft group developed a periprosthetic fracture and developed an infection after treatment of this fracture.

Infection is the major cause of failure in revision TKA (44.1%) [69] and the risk is even higher in patients with septic revisions.[69,82] However, given the absence of any prospective controlled studies, the paucity of comparative studies with control groups, and the conflicting data in case series, we could not reach any conclusion regarding the effect of using an allograft on the rate of infection in revision arthroplasty for septic failures.

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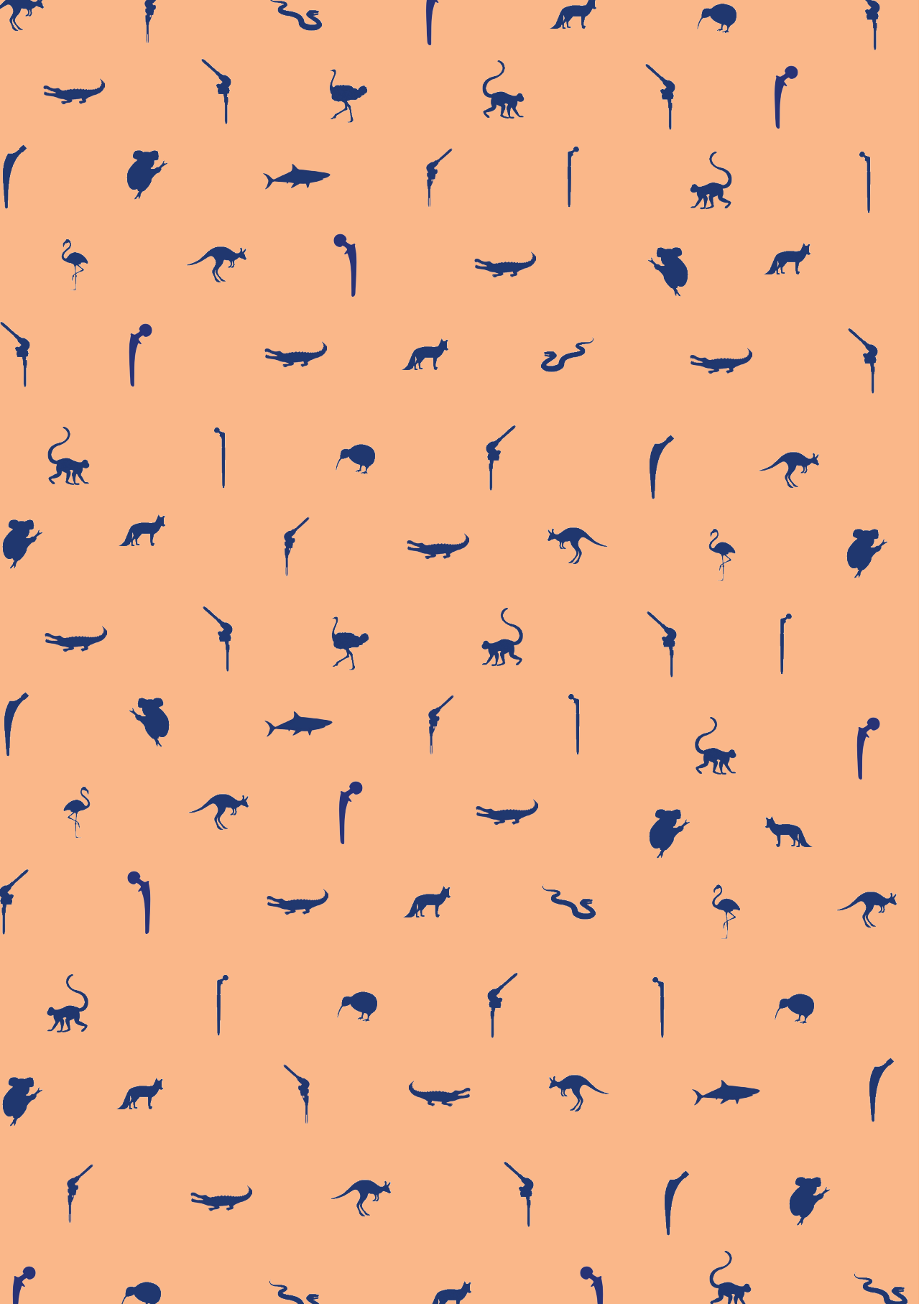
SECTION

3



CHAPTER

6

Similar rate of infection eradication for functional articulating, prefabricated and custom–made spacers in two-stage revision of the infected total hip

A literature review

(Hip International. 2016; 26 (4): 319-326)

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ABSTRACT

Background Nowadays, two-stage revision with the use of an antibiotic-loaded interval spacer is therapy of choice in late periprosthetic joint infection for most surgeons. For the spacer, either a prefabricated, functional articulating or custom made spacer can be used. Little is known about which type of spacer provides optimal outcome after two-stage revision. The aim of this study was to determine which type of spacer provides the best results, when used in two-stage revision of an infected THA.

Methods We performed a systematic review of the literature to analyse which type of interval spacer provides highest infection eradication rate and best functional outcome after a minimum two year follow-up. Exclusion criteria were follow-up of less than 2 years, single-stage revision, or two-stage revision without use of a spacer.

Results Twenty-five studies were included. Infection eradication rate was similar with rates of 96%, 93% and 95% for the prefabricated-, functional articulating- and custom made spacers respectively. Functional outcome was scarcely described. Postoperative HHS was 81, 90 and 83 respectively.

Interpretation Functional articulating spacers achieve a comparable rate of infection eradication in the treatment of periprosthetic hip joint infections as compared to preformed or custom-made antibiotic-loaded spacers. There is insufficient evidence concerning rehabilitation and functional outcome after two-stage revision hip arthroplasty to advocate or discourage the use of either kind of interval spacer.

Keywords: antibiotic-loaded spacer, functional articulating spacer, periprosthetic joint infection, total hip arthroplasty, two-stage revision.

INTRODUCTION

Periprosthetic joint infection (PJI) is a devastating complication after primary and revision arthroplasty. The number of total knee and hip arthroplasties performed yearly is expected to increase drastically in the coming decades.[1] Even if the percentage of PJI can be decreased, this will cause an increase in the absolute number of PJI requiring treatment. This development asks for standardized evidence based protocols describing the best type of treatment for PJI. Debridement, antibiotics and implant retention are treatment of first choice in case of early infection after total hip arthroplasty (THA).[2, 3] In case of late or persisting infection, one- or two-stage revision needs to be performed according to global consensus.[3, 4] The use of different kinds of spacers in two-stage revision surgery has been widely debated in the past years.[5, 6] Various preformed spacers are available, as well as functional articulating spacers and spacers custom made by individual surgeons following a local protocol.

The aim of this study was to determine which type of spacer should be used during the interval of two-stage revision of an infected THA. First, we hypothesize that functional articulated spacers achieve infection eradication results comparable to other types of spacers. Second, we hypothesize that the rehabilitation period is shorter and patients' functional outcome is improved after two-stage revision with the use of a functional articulated spacer. In addition, we compared the incidence of spacer-related complications between the groups.

METHODS

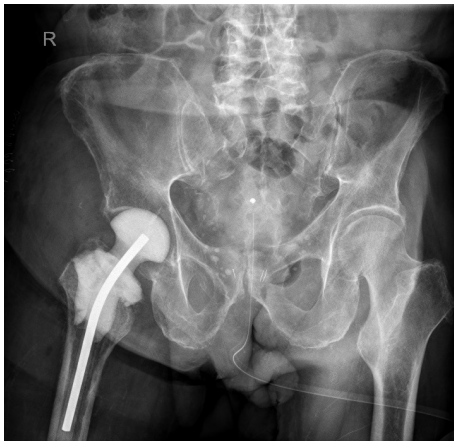
A review protocol was constructed and registered at PROSPERO international prospective register of systematic reviews (http://www.crd.york.ac.uk/PROSPERO/) with reference number CRD42014014324.

The search term can be found in appendix 1. The search was limited to adult humans and the databases (Pubmed/Medline, Embase, and Cochrane Library) were searched from 1978 to April 1st 2015. The lists of references of retrieved publications were manually checked for additional studies potentially meeting the inclusion criteria and not found by the electronic search. One-stage revision, two-stage revision without use of a spacer, in vitro studies and studies with a follow-up of less than two years were exclusion criteria. Studies on objective or functional outcome were selected and more closely reviewed by one of the authors (EV) and verified by a second author (DJM).

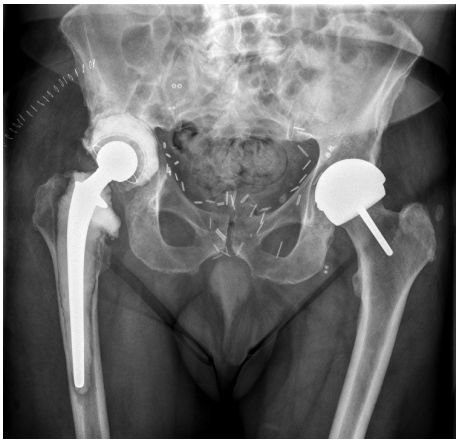
We extracted all information regarding the level of evidence, mean years of follow-up, number of patients initially included in the study and the number of patients available for follow-up, baseline patient characteristics and baseline clinical and laboratory findings. Data regarding type of spacer and antibiotics used, timing of second stage surgery, tissue culture results, postoperative regimen, functional outcome and patient satisfaction were extracted. The type of spacer was identified and studies were divided into three groups. Group I comprised studies using a preformed spacer (such as the Spacer-G) (figure 1A), group II comprised studies using a functional articulating spacer (Figure 1B) and group III comprised studies using a custom made spacer either from a prefabricated template or manufactured by the individual surgeons following a local protocol.

Figure 1

A. postoperative radiograph of a patient with a prefabricated antibiotic-loaded hip spacer of the right hip.



B. postoperative radiograph of a patient with an antibiotic-loaded functional articulated spacer of the right hip.



A spacer is considered a functional articulating spacer when patients are encouraged to bear partial to full weight and rehabilitation is stimulated. Functional articulating spacers consist of (parts of) regularly used prosthetic hip devices combined with antibiotic cement. An example is the PROSTALAC spacer. A spacer is considered a custom made spacer when a mold (either prefabricated or constructed by the authors of the original article) is used intraoperatively to construct a cement spacer, with or without the addition of any kind of internal stabilization.

The data included in the articles were extracted by one author (EV) and verified by a second (DJM). Primary outcome was success rate of infection eradication, defined as retention of the revision prosthesis at final follow-up without signs of recurrent infection. Secondary outcomes were the number of adverse events or complications and patient satisfaction and functional recovery as measured by patient reported outcome measures (PROMs).

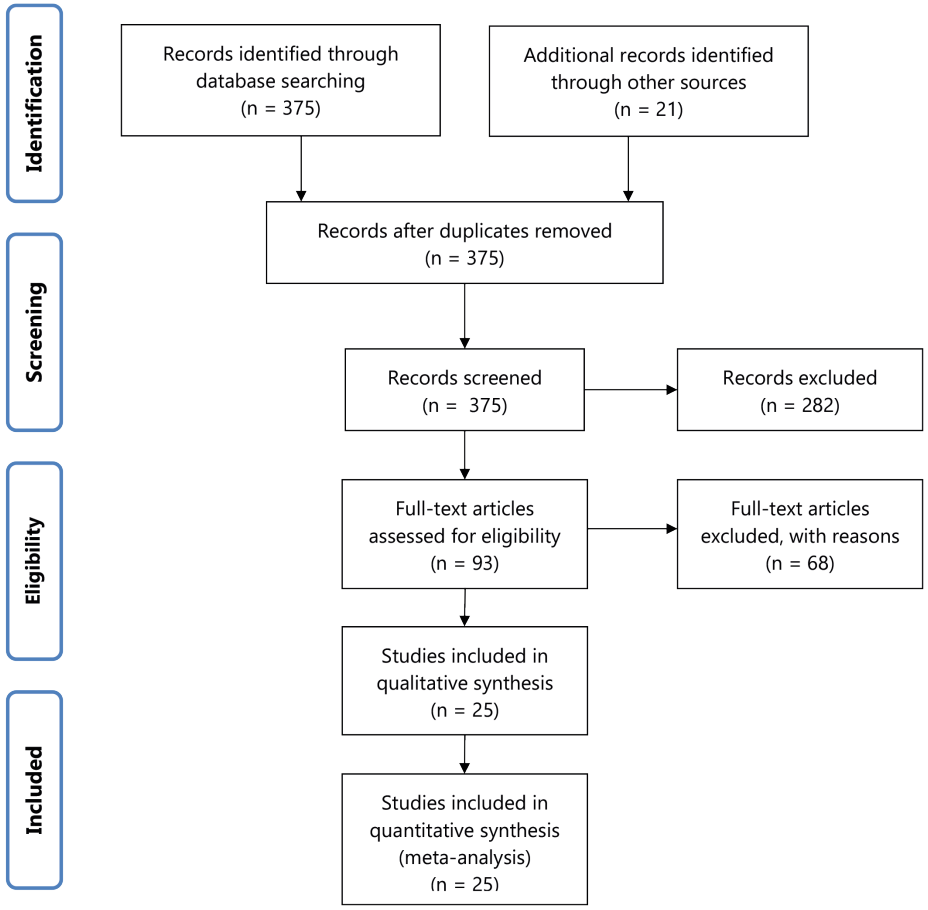
Studies were graded according the scoring system of the Grading of Recommendations Assessment, Development and Evaluation (GRADE) working group (http://www.gradeworkinggroup.org/index.htm). In short, for studies on therapy or prognosis, Level I is attributed to well designed and performed randomized controlled trials, Level II are cohort studies, Level III are case–control studies, Level IV are case series and Level V are expert opinion articles.

RESULTS

The search resulted in a total of 375 related studies, of which 93 studies were selected for additional review of the full text. A total of twenty-five studies met our inclusion criteria and were included for data analysis (Figure 2).[4, 7-30] The studies were published from 1997 to 2014. General characteristics of the included studies can be found in table 1. All reported averages in Table 3 are sample size weighted. Pooling of the overall results was not possible due to the clinical heterogeneity of the data. As a consequence no statistical analysis could be performed. Outcome after treatment will also depend on extent of infection, delay in treatment, virulence and susceptibility of infecting agents, quality of surgical debridement, type and extent of antibacterial treatment, compliance with treatment and so on. These potential confounders were in general poorly reported and when described heterogeneity of these factors was too large to analyze the effect on outcome.

Seven studies described preformed spacers, eight studies described functional articulating spacers and ten studies described custom made spacers. The only functional outcome measure used both pre- and postoperatively in at least one study per group was the Harris Hip Score (HHS)[31], outcome measures used only pre- or postoperatively were not further analyzed.

Figure 2: PRISMA flow diagram



Group I; prefabricated spacers

A total of 389 patients in seven studies were treated with two-stage revision of an infected hip arthroplasty with the use of a prefabricated antibiotic-loaded spacer.[9, 17, 19, 21-23, 30] In all studies the Spacer-G/Interspace was used. Characteristics of the patients, type of spacer, causative micro-organisms and complications can be found in tables 1, 2 and 3. Re-infection occurred in 4% of patients, resulting in a treatment success rate of 96% (range 80-98%). Mean interval between the first and second stage procedure was thirteen weeks. The second stage procedure was performed in 97% of originally included patients. Mean preoperative HHS was 28, which improved to 84 postoperatively after the second stage.[22, 23]

Group II; functional spacers

A total of 527 patients in eight studies were treated with two-stage revision of an infected hip arthroplasty with the use of a functional articulating antibiotic-loaded spacer.[7, 11, 12, 16, 18, 25, 26, 29] Characteristics of the patients, type of spacer, causative micro-organisms and complications can be found in tables 1, 2 and 3. Re-infection occurred in 7% of patients, resulting in a treatment success rate of 93% (range 76-100%). Mean interval between the first and second stage procedure was sixteen weeks. The second stage procedure was performed in 89% of originally included patients. Patients retaining the functional spacer were not accounted for when calculating time between first and second stage. Mean preoperative HHS was 53, which improved to 90 postoperatively after the second stage.[32]

Group III; custom made spacers

A total of 534 patients in ten studies underwent two-stage revision with the use of a custom made spacer.[4, 8, 10, 13-15, 20, 24, 27, 28] The study by Hsieh et al describes two groups of patients, which were both included in this study and were analysed separately.[14] In six studies prefabricated molds were used, in the other five studies spacers were intra-operatively molded by hand. Spacers were enforced by K-wires in four studies, by a Küntscher nail in 2 studies, by a rush pin in two studies and by a modular head and stem in one study. In two studies no reinforcement was used. Characteristics of the patients, type of spacer, causative micro-organisms and complications can be found in tables 1, 2 and 3. Re-infection occurred in 5% of patients, resulting in a treatment success rate of 95% (range 86-100%). Mean interval between the first and second stage procedure was eleven weeks. The second stage procedure was performed in 97% of originally included patients. Mean preoperative HHS was 39, which improved to 81 postoperatively after the second stage.[4, 13, 20]

Table 1; General characteristics

Author	Year	Level of evidence	N of hips stage 1	Age	M	F	Type of spacer	N of hips stage 2	Failure	Success (%)	Patients available for follow-up (n)	FU (months)
Group 1; Prefabricated spacers												
Cherubino	2013	3	30	71	17	13	Spacer-G/InterSpace	29	1	97	30	72
Magnan	2001	4	10	72	7	3	Spacer-G/InterSpace	8	2	80	10	35
Neumann	2012	4	44	x	25	19	Spacer-G/InterSpace	42	1	98	44	67
Pattyn	2010	3	61	65	30	31	Spacer-G/InterSpace	61	2	96	61	36
Pignatti	2010	4	41	59	16	25	Spacer-G/InterSpace	40	1	98	41	64
Romano	2011	3	20	56	9	11	Spacer-G/InterSpace	20	1	95	20	57
Romano	2012	4	183	60	61	122	Spacer-G/InterSpace	183	10	94	162	60
Group 2; Functional spacers												
Biring G	2010	3	99	72	52	47	Prostalac	48	4	89	48	144
Fink	2009	4	44	69	20	16	Functional spacer	39	0	100	39	35
Hofmann	2005	4	42	64	15	12	Functional spacer	35	1	96	27	76
Leung	2011	4	50	64	20	18	Prostalac	38	9	76	38	58
Masri	2007	4	31	65	21	10	Prostalac	29	3	90	29	47
Tsung	2014	4	76	72	37	38	Functional spacer	42	12	84	76	80
Wentworth	2002	3	135	66	66	69	Functional spacer	118	24	83	135	x
Younger	1997	4	50	67	22	28	Functional spacer	48	3	94	50	43

Table 1; General characteristics (continued)

Author	Year	Level of evidence	N of hips stage 1	Age	M	F	Type of spacer	N of hips stage 2	Failure	Success (%)	Patients available for follow-up (n)	FU (months)
Group 3; Custom made spacers												
Cabrita	2007	1	38	54	x	x	Custom spacer	33	4	89	38	48
Durbhakula	2004	3	20	70	12	8	Custom spacer	18	2	90	20	38
Hsieh	2004	3	42	61	32	10	Custom spacer	40	3	93	42	55
Hsieh Group 1	2009	4	51	59	27	19	Custom spacer	49	4	91	49	50
Hsieh Group 2			56	62	33	20	Custom spacer	53	4	89	53	37
Ibrahim	2014	3	125	68	x	x	Custom spacer	125	5	96	125	103
Klouche	2012	3	46	67	26	20	Custom spacer	46	4	91	46	35
Oussedik	2010	4	39	x	x	x	Custom spacer	39	2	96	39	60
Schwartzkopf	2014	4	56	62	27	29	Custom spacer	48	8	86	56	32
Whittaker	2009	4	44	69	21	22	Custom spacer	44	5	93	44	49
Yamamoto	2003	4	17	62	6	11	Custom spacer	17	0	100	17	38

n = number; M = male; F = female; X = not reported

Table 2: bacteria isolated at first stage procedure.

Author	S. epidermidis	S. aureus	MRSA/ MRSE	E. faecalis	Multiple Gram+	Strep species	Gram– (undefined)	E. coli	P. aeruginosa	negative cultures	Other
Group I											
Cherubino	5	8			5	2		2		8	
Magnan	1	1				1	1	1	1	4	
Neumann	6	10	5			7	2	2	2		7
Pattyn	13	14	8	1	4	6				11	4
Pignatti	8	7	9	2	10	1				4	
Romano	3	7	4	1					1	4	
Romano	36	38	38	5			13	5	14	68	13
Total	**51**	**85**	**64**	**9**	**19**	**17**	**16**	**10**	**18**	**99**	**24**
Group II											
Biring	26	22	10		20	12	10	3		5	1
Fink	25	4	3	7		1	4				3
Hofmann	1	6	3	2		1	2	1	2	5	
Leung F			38								
Masri	10	11	1	1	3	1	2				
Tsung	30	16	3	2	1	8	3	4	2	7	1
Wentworth	38	28				4	2	2			21
Younger	24	7			2	9	3	1	1		1
Total	**86**	**94**	**58**	**12**	**26**	**36**	**26**	**11**	**5**	**17**	**27**

Table 2: bacteria isolated at first stage procedure. (continued)

Author	S. epidermidis	S. aureus	MRSA/ MRSE	E. faecalis	Multiple Gram+	Strep species	Gram– (undefined)	E. coli	P. aeruginosa	negative cultures	Other
Group III											
Cabrita	10	23		10		6	23	4	1		3
Durbhakula	4	6	2	2		4		1			1
Hsieh	9	14		2	3		4	3	6		1
Hsieh Gr1	11	4	12	1	1	3	3	2	5	4	
Hsieh Gr2	10	5	15	1	2	2	2	5	8	3	
Ibrahim	35	29	14		16	11	19			13	7
Klouche	12	5	12	1	4	5					7
Oussedik	19	3	6		6		2	3	3		
Schwartzkopf	2	13	1		2	6	2		1	16	22
Whittaker	27	3	2	7		5					
Yamamoto	8		3					1	1	4	
Total	**48**	**105**	**67**	**24**	**34**	**42**	**55**	**19**	**25**	**40**	**41**

Table 3: Complications.

Complication	Group 1	Group2	Group 3
After 1st stage			
Spacer dislocation	13%	4%	3%
Spacer fracture	0%	0%	2%
Femur fracture	4%	4%	1%
Re-infection during spacer	5%	6%	14%
Repeat 1st stage procedure	5%	3%	6%
After 2nd stage			
Re-infection after 2nd stage	4%	7%	5%
Recurrent dislocation	2%	3%	2%
Revision for infection	2%	4%	2%

All shown numbers are percentage per group.

DISCUSSION

The aim of this study was to perform a systematic review of the literature to investigate which type of antibiotic-loaded spacer provides the best outcome in patients treated with two-stage revision for an infected arthroplasty of the hip. Our first hypothesis was that functional spacers would provide a comparable rate of infection control as compared to custom made or preformed antibiotic-loaded spacers. Our results show comparable good results for the three types of spacers when considering infection control, with control rates ranging between 93% and 96%. Patients receiving antibiotic suppression therapy after two-stage revision were considered failure of treatment.

Our second hypothesis was that patients treated with a functional spacer would experience a shorter rehabilitation time and better functional results as compared to patients treated with custom made or preformed antibiotic-loaded spacers. While functional and patient reported outcome after primary total hip arthroplasty has extensively been described in literature, functional outcome after revision total hip arthroplasty for PJI has scarcely been reported. Of all included studies only one study[17] describes postoperative range of motion, no studies report patient satisfaction. The only frequently used outcome measure was the HHS, which showed comparable postoperative scores in all groups. Other outcome measures were used less than twice per group and gave insufficient data to compare between groups of spacers. The original studies did not report on rehabilitation protocols. We had insufficient data to prove or disprove our second hypothesis.

Most complications are evenly distributed among the three groups, except for dislocation. The incidence of spacer dislocation is high in the prefabricated spacer group as compared to both other groups (13% versus 4% and 3% respectively). Although this appears to be a large difference, significance levels could not be calculated, due to heterogeneity of the original data. The difference can be explained by the possibility for the orthopaedic surgeon to adjust functional spacers and custom made spacers to the situation in an individual patient, considering for instance femoral shaft size, neck length, offset deficiency, acetabular size or bone loss. The prefabricated spacers are only available in a limited number of sizes resulting in overstuffing or instability in some patients, which might lead to spacer dislocation.

Remarkably, in 11% of patients in group 2 no second stage procedure was performed. This high incidence was caused by patients refusing second stage surgery because they were satisfied with the functional result after first stage placement of the functional articulating spacer. Outcome measures and functional results such as walking distance and range of motion were not specifically reported for the group of patients refusing second stage surgery.

There are differences in bacteriology between the three groups. Group 1 contains a high number of culture negative cases, especially in the study by Romano et al.[30] These patients might have a positive influence on the outcome, as infection has not been objectified during primary surgery and bacteria might have been absent in the patients.

A weak point of this study is the lack of quality of evidence. There is an absence of level 1 evidence comparing different kinds of spacers in the two-staged treatment of PJI of the hip. Functional outcome and patient satisfaction after one- or two-stage revision of the infected total hip arthroplasty have only scarcely been described and therefore could not be presented in the results. Also, due to the lack of information in and heterogeneity of the original data concerning extent of infection, delay in treatment, virulence and susceptibility of infecting agents, quality of surgical debridement, type and extent of antibacterial treatment, compliance with treatment, type of antibiotic in the spacer cement and timing of second stage procedure the effect of these factors on outcome could not be analyzed. We acknowledge these could be confounding factors.

This study creates a comprehensive overview of the available literature on the use of antibiotic-loaded spacers in two-stage revision arthroplasty of the infected prosthetic hip joint. With the challenge of an increasing number of infected total hip revisions

ahead, there is a need for an evidence based approach to the treatment of PJI after total hip arthroplasty. Literature comparing functional outcome between various spacers in two-stage revision of the hip is absent. Various studies have investigated the outcome of one-stage versus two-stage revision arthroplasty[6] or difference in outcome of two-stage revision with the use of different types of spacers including cement beads and Girdlestone procedures.[5, 15, 33-36] None of these studies have described functional outcome after revision arthroplasty of infected total hip arthroplasty.

Functional spacers may improve the congruence of the joint compared to preformed spacers, but up to date there have been no reports investigating whether clinical performance during and after two-stage revision is better with a functional spacer.

The international consensus meeting[3] concerning periprosthetic joint infections organized in 2013 resulted in the following statements: (1) the type of spacer does not influence the rate of infection eradication in two-stage exchange arthroplasty of the hip, (2) a period of antibiotic therapy of 2 to 6 weeks after removal of the infected implant is recommended, (3) there is no definitive evidence in the literature as to the optimal time interval between the two stages, reports vary from 2 weeks to several months. As could be expected after reading the recommendations from the international consensus meeting, we have found a large variety in treatment protocols described in literature.

Research should focus on finding the preferred type of treatment and type of spacer to combine a high success rate of infection treatment with a good functional and patient reported outcome. There is a need for a large, prospective study evaluating patient satisfaction and functional outcome after two-stage revision hip arthroplasty comparing various kinds of antibiotic-loaded spacers. Secondly, research should focus on the optimal timing of the second stage procedure.[37]

Functional articulating spacers achieve a comparable rate of infection eradication in the treatment of periprosthetic hip joint infections as compared to preformed or custom-made antibiotic-loaded spacers. There is insufficient evidence concerning rehabilitation and functional outcome after two-stage revision hip arthroplasty to advocate or discourage the use of either kind of interval spacer.

CONTRIBUTION OF AUTHORS

All authors have made substantial contributions to study design, data collection, manuscript draft and/or manuscript revision.

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CONFLICT OF INTEREST AND FUNDING

No funding was received for this study. We have no conflict of interest to mention.

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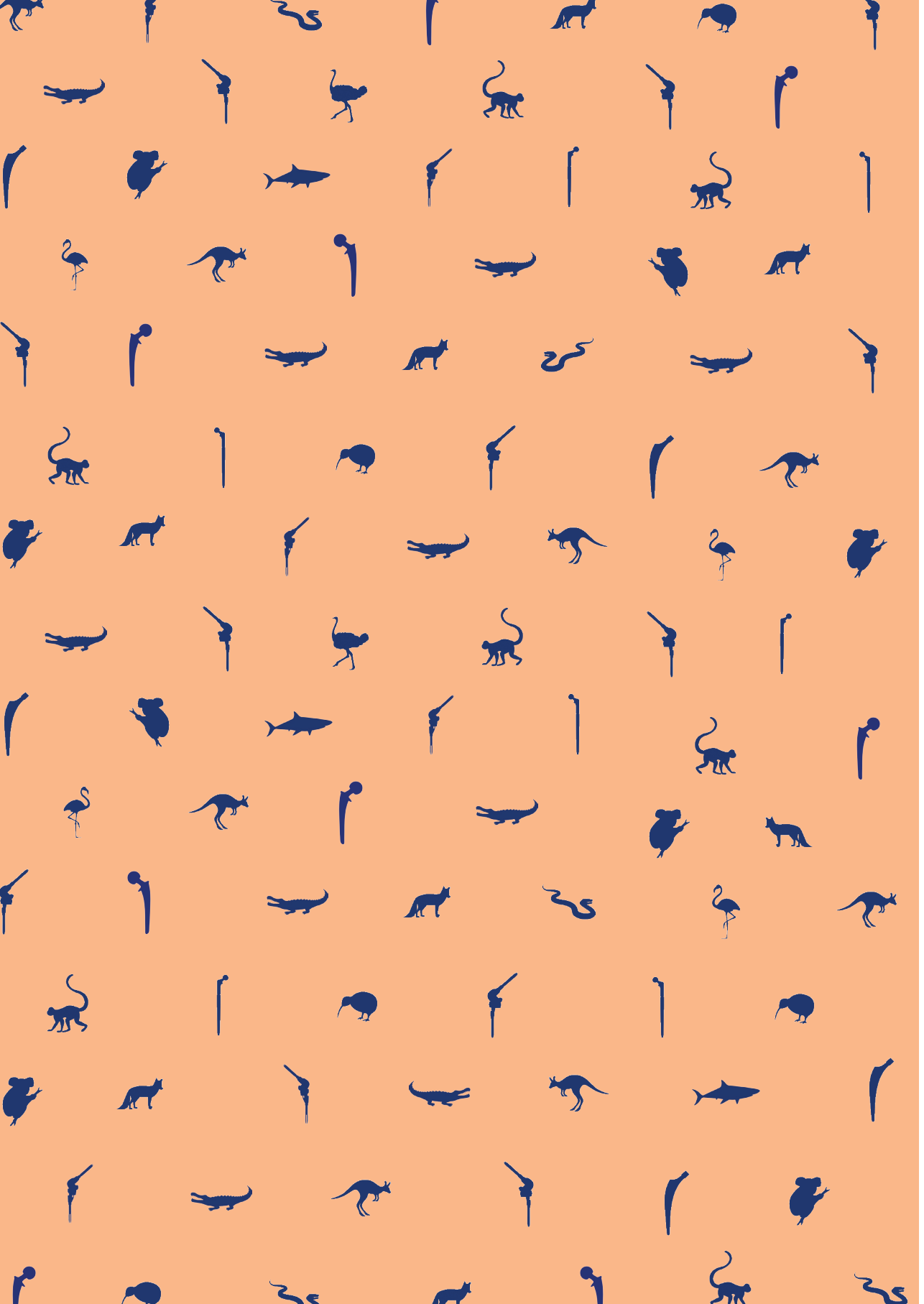
APPENDIX 1:

A search term with Boolean operators was constructed: ((spacer[all fields] OR two-stage[all fields]) AND (((“hip”[MeSH Terms] OR “hip”[All Fields]) AND (“arthroplasty”[MeSH Terms] OR “arthroplasty”[All Fields])) OR (“arthroplasty, replacement, hip”[MeSH Terms] OR (“arthroplasty”[All Fields] AND “replacement”[All Fields] AND “hip”[All Fields]) OR “hip replacement arthroplasty”[All Fields] OR (“total”[All Fields] AND “hip”[All Fields] AND “replacement”[All Fields]) OR “total hip replacement”[All Fields]))) AND ((“infection”[MeSH Terms] OR “infection”[tiab] OR “infections”[tiab]) OR (revision[All Fields] AND (“hip”[MeSH Terms] OR “hip”[All Fields]))).



CHAPTER

7

Improved Patient Reported Outcome and Infection Eradication Rate with Functional Articulating Spacers in Two-Stage Revision of the Infected Hip

(submitted)

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ABSTRACT

Introduction Two-stage revision arthroplasty with an antibiotic-loaded spacer is treatment of choice in chronically infected total hip arthroplasties. Interval spacers can be functional articulating or prefabricated. Functional results of these spacers have scarcely been reported. We retrospectively compared patient reported outcome and infection eradication rate after two-stage revision arthroplasty for periprosthetic joint infection of the hip with the use of a functional articulating or prefabricated spacer.

Materials and Methods All patients with two-stage revision of a hip prosthesis between 2003 and 2016 were retrospectively included. Patients were divided into two groups; patients treated with a functional articulating spacer or with a prefabricated spacer. Patients completed the Hip Osteoarthritis Outcome Score and the EQ-5D and EQ-VAS scores. Primary outcomes were patient reported outcome and infection eradication after two-stage revision. The results of both groups were compared to the patient acceptable symptom state (PASS).

Results We consecutively treated fifty-five patients with a prefabricated spacer and fifteen patients with a functional articulating spacer of the hip. Infection eradication rate for functional articulating and prefabricated spacers were 93% and 78% respectively. More patients in the functional articulating spacer group reached the PASS for the HOOS pain, HOOS QoL and EQ-VAS.

Conclusions Functional articulating spacers seem to lead to improved patient reported functional outcome, better infection eradication rate and less perioperative complications after two-stage revision arthroplasty of an infected total hip prosthesis, compared to prefabricated antibiotic-loaded spacers.

Failure of two-stage revision and subsequent explantation of the prosthesis leads to very poor quality of life.

Keywords: Periprosthetic joint infection; total hip arthroplasty; functional articulating spacer; hip revision.

INTRODUCTION

When a periprosthetic joint infection (PJI) persists after a debridement, antibiotics and implant retention procedure of an infected prosthesis, or when onset of infection is delayed or late, the PJI is considered chronic.[1, 2] Two-stage revision arthroplasty is the standard treatment for chronic PJI of the hip.[3] Antibiotic-loaded interval spacers have proven to be effective in eradicating the infection.[3-5] In contrast to a Girdlestone situation the antibiotic-loaded hip spacer keeps the soft tissues at length during the interval period.[6] Antibiotic-loaded interval spacers can be either functional articulating, prefabricated or custom-made peroperatively with or without the use of a prefabricated mold.[4] The infection eradication rates for these types of spacers are comparable, while the complication rates of prefabricated spacers are reported to be higher.[4, 7, 8] Dislocation of prefabricated hip spacers is the most common complication occurring during the spacer interval, which is probably caused by the limited number of options available to adjust the prefabricated spacer to the patients' anatomy.[4]

Repetitive surgery on a joint causes soft tissue trauma, which can lead to periarticular fibrosis and impaired range of motion.[6, 9] Therefore, orthopaedic surgeons have been trying to find a type of antibiotic-loaded spacer with the same efficacy in infection eradication, but also facilitating range of motion exercises and ambulation during the spacer period.[7, 10, 11] Since the functional articulating spacers allow the patient normal activity during the interval period, they may be a good solution for these functional problems and thereby also decrease morbidity and impairments of the patients to a certain extent. Patient related functional assessment of hip function after two-stage revision of the infected total hip arthroplasty (THA) with the use of a functional articulating has only scarcely been reported, and these studies did not compare the outcome of the different types of spacers.[10, 11]

We retrospectively reviewed all patients treated with two-stage revision of an infected hip arthroplasty with the use of either a prefabricated or a functional articulating spacer between 2003 and 2016. We hypothesized functional articulating spacers lead to improved patient reported outcome, fewer complications and shorter in-hospital stay, while maintaining a comparable infection eradication rate as compared to prefabricated antibiotic-loaded hip spacers.

METHODS

The STROBE statement was adhered to while constructing the study and writing the manuscript.

Patients

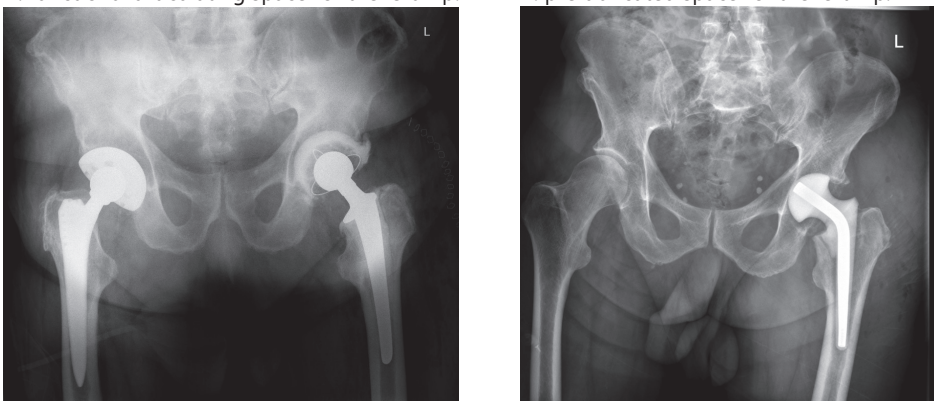
After approval by the local medical ethics committee, the records of all patients whom had two-stage revision arthroplasty of the hip between 2003 and 2016 were retrospectively reviewed. All patients with chronic periprosthetic joint infection of the hip that were treated with two-stage revision arthroplasty with the use of an interval spacer and with follow-up of at least twelve months were included in the study. Exclusion criteria were two-stage revision without the use of a spacer, patients treated with one-stage revision and follow-up of less than twelve months. Extent of bone loss was not an exclusion criterion for either kind of spacer.

Intervention

During first-stage surgery the infected prosthesis including bone cement, if present, was removed using a posterolateral approach. After meticulous debridement a functional articulating - or a prefabricated antibiotic-loaded interval spacer was inserted (Figure 1A and 1B, respectively). The functional articulating spacers are made of commonly used femoral and acetabular cemented components. During insertion the antibiotic-loaded cement is not pressurized and care is taken to have no cement distal to the tip of the stem. The type of antibiotics used in the cement can be adjusted to the causative pathogen found in the preoperative cultures. The surgeon has several options to optimize offset and neck length of the femoral component, and offset, version and inclination of the acetabular component. The spacer enables patients to practice full range of motion and patients are allowed to walk bearing 50% to full body weight, irrespective of the extent of bone loss. Prefabricated antibiotic-loaded hip spacers are commercially available with different stem lengths and head sizes. During the spacer interval the prefabricated spacer allows patients to practice range of motion of the hip. Weight-bearing during the spacer interval is usually limited to less than 25% of body weight. The two groups of patients were treated consecutively, there were no differences in selection criteria for either type of treatment. Initially the prefabricated spacers were used, later the functional articulating spacers. The concentration of antibiotics in the cement were the same in both groups.

All included patients were treated with antibiotics according to the recommendations postulated by Zimmerli and colleagues in 2004.[2] The type of antibiotic treatment was decided in close consultation with a microbiologist and an infection specialist. Two weeks before the second stage procedure antibiotics were discontinued to achieve a two-week antibiotic free interval. During the study period there were no other changes to the treatment practice, except for the implementation of the functional articulating spacers in 2014.

Figure 1
A. functional articulating spacer of the left hip. B. prefabricated spacer of the left hip.



Data and Patient Reported Outcome Measures

General patient characteristics, complications during treatment and infection status were retrieved from patients' records. At follow-up patient reported outcome was measured using the Hip Osteoarthritis Outcome Score (HOOS), EQ-5D-3L (EQ5D) and the EQ-5D quality of life thermometer (EQ-VAS) were used to assess patient reported outcome.[12, 13] The HOOS is a validated score for patients with osteoarthritis of the hip and consists of five domains: symptoms (5 questions), pain (10 questions), activities (17 questions), sports (4 questions) and quality of life (4 questions). Using all answers a score can be calculated with range of scores between 0-100, with 100 as the optimal score. The EQ-5D is a questionnaire that is developed to describe and value health across a wide range of disease areas. The EQ-5D comprises of 5 dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. The patient indicates his health state on one of three levels: no problems, some problems or extreme problems, labelled 1-3. The scores can be converted into a value -0.500 to 1.00, with 1.00 as the optimal score. The EQ-5D also contains a visual analogue scale for quality of life (EQ-VAS), where patients can indicate their perceived quality of life on a range of scores 0-100, with 100 as the optimal score.

Primary outcomes were patient related outcome measure scores (PROMs) and infection eradication after second-stage procedure. Secondary outcomes were complications reported during the spacer period and at final follow-up.

Data analysis

The results of the subscores of the HOOS and the result of the EQ-5D were compared to the patient acceptable symptom state (PASS) as described for patients following

primary total hip arthroplasty by Paulsen and colleagues.[14] The PASS for the HOOS, EQ-5D and EQ-VAS are 91 (HOOS Pain), 88 (HOOS-PS), 83 (HOOS QoL), 0.92 (EQ-5D Index), and 85 (EQ-VAS), respectively.[14]

Patients were analyzed for the type of spacer they were treated with. To be able to compare patient reported outcome after successful treatment and to determine patient reported outcome after failed two-stage revision and subsequent treatment, the PROMs of successfully and unsuccessfully treated patients were analyzed separately.

Failure of treatment was defined as persisting infection at final follow-up, removal of the hip prosthesis or use of suppressive antibiotics at follow-up.[15] Descriptive statistics, mean and range are used to represent the demographics of the patients. For numerical variables we used students' t-tests were used to assess the level of significance for differences between the groups, with 95% confidence intervals, for binary outcome we used Fisher's exact test. Calculations and statistical analyses were performed using Excel and SPSS software.

RESULTS

Patient characteristics and general outcome

Between 2003 and 2016 we consecutively treated fifty-five patients with a prefabricated spacer and fifteen patients with a functional articulating spacer. General patient characteristics and infection characteristics are listed in Table 1 and 2. All live patients completed the PROMs. The results of HOOS and EQ-5D scores are displayed in Figure 2.

Table 1: General patient characteristics

	Functional articulating spacer group	Prefabricated spacer group	p
Number of patients	15	55	
Age (range)	66 (58-76)	68 (33-88)	N.S.
Gender female	8	25	N.S.
BMI (range)	27 (20-35)	27 (19-41)	N.S.
BMI > 30	3	13	N.S.
Diabetes	4	8	N.S.
ASA 1/2/3	1 / 11 / 3	3 / 30 / 22	N.S.
Post-traumatic (fracture)	6	9	< 0.05
Months follow-up (range)	24 (16-85)	51 (13-129)	< 0.005

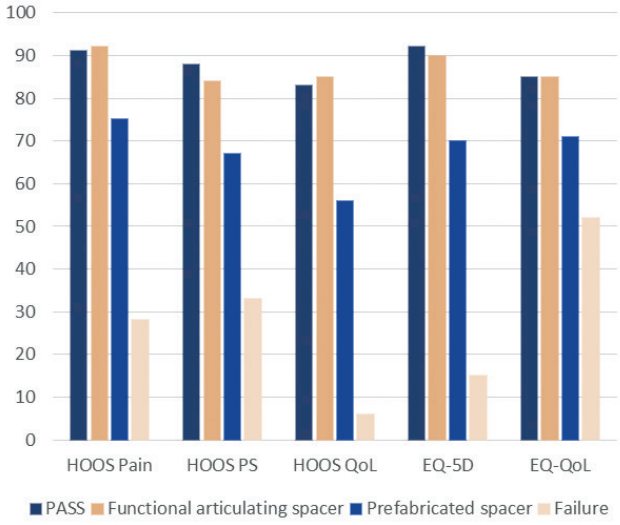
N.S. = Not significant. BMI = Body mass index. ASA = American Society of Anesthesiologists score.

Table 2: Infection characteristics, causative pathogens

	Functional articulating spacer group	Prefabricated spacer group
CoNS	10	18
S. aureus	0	9
S. epidermidis	0	1
Propioni Acnes	0	5
E. faecalis	2	2
E. coli	0	1
P. aeruginosa	0	1
H. parainfluenzae	0	1
Corynebacterium	0	2
Aerococcus christensenii	0	1
Group B Streptococcus	1	0
Candida albicans	0	2
Culture negative	0	4
Polymicrobial	2	8

CoNS = *Coagulase Negative Staphylococcus.*

Figure 2: patient reported outcome measure results at follow-up



The results of the EQ5D score are multiplied by 100 for reasons of readability.
HOOS = Hip Osteoarthritis Outcome Score
PASS = Patient Accepted Symptom Scale as described by Paulsen [14].
QoL = Quality of life.

Functional articulating spacer group

Fifteen patients were treated with a functional articulating spacer of the hip. At a mean follow-up of 24 months (range 15-85 months) one patient had died due to reasons unrelated to treatment.

The mean operating time of the first-stage surgery was 160 minutes (range 116-290 minutes). Patients were admitted to the orthopaedic ward for median thirteen days (range 5-34 days) after the first stage procedure. Spacer dislocation occurred in two patients. Both patients experienced one dislocation each, which was treated with a closed reduction in both patients. The mean duration of the spacer interval was eight weeks (range 5-12 weeks).

The mean operating time of the second stage surgery was 139 minutes (range 88-188 minutes). After the second stage procedure patients were admitted for a median six days (range 3-12 days) postoperatively. Results of the PROMs are listed in Table 3 and Figure 2, PASS was reached for the mean score of the HOOS pain, HOOS QoL and EQ-VAS.

We consider one patient as failure of treatment. Infection persisted after two-stage revision, therefore a Girdlestone situation was created.

Table 3: Patient reported outcome measure results and comparison of the groups.

	Functional articulating spacer group	Prefabricated spacer group	p
Number of patients	15	55	
HOOS total (SD)	88 (6)	67 (14)	<0.01
HOOS pain (SD), % PASS	92 (6), 54%	75 (14), 8%	<0.01
HOOS PS (SD), % PASS	85 (6), 15%	67 (14), 3%	<0.01
HOOS QoL (SD), % PASS	85 (12), 46%	56 (21), 5%	<0.01
EQ-5D (SD), % PASS	0.90 (0.17), 46%	0.69 (0.30), 5%	<0.01
EQ-VAS (range), % PASS	85 (65-100), 46%	71 (45-85), 3%	<0.05

HOOS = hip osteoarthritis outcome score. PASS = patient acceptable symptom state. QoL = quality of life. VAS = visual analogue scale.

Prefabricated spacer group

Fifty-five patients were treated with a prefabricated spacer of the hip. At a mean follow-up of 51 months (range 13-129 months) ten patients had died, five of these patients had died due to reasons unrelated to treatment.

The mean operating time of the first-stage surgery was 186 minutes (range 70-360 minutes). Patients were admitted to the orthopaedic ward for median thirty-one days (range 5-114 days) after the first stage procedure. Ten patients experienced dislocation of the spacer. In these ten patients a total of twenty-five dislocations occurred. Revision of the spacer because of multiple dislocations was performed in seven patients. The mean duration of the spacer interval was eight weeks (range 2-28 weeks).

The mean operating time of the second stage surgery was 165 minutes (range 75-326 minutes). After the second stage procedure patients were admitted for a median twenty-two days (range 3-63 days) postoperatively. After the second-stage procedure dislocation of the hip prosthesis occurred in two patients, both of these patients were treated with a closed reduction. Results of the PROMs are listed in Table 3 and Figure 2, none of the mean outcomes reached the PASS.

We considered twelve patients as failure of treatment. Persistent infection occurred in eight patients, re-infection with a different bacteria was present in four patients. Two patients were treated with lifelong suppressive antibiotics. Two patients underwent subsequent two-stage revision which was successful in both. Eventually a Girdlestone situation was created in eight patients. Five of the failure patients had died at time of final follow-up.

Comparison of the groups

With respect to the functional outcome, the HOOS and its subscores (all $p<0.01$), the EQ-5D ($p<0.01$) and the EQ-VAS scores ($p<0.05$) were all significantly better for patients successfully treated with a functional articulating spacer compared to patients successfully treated with a prefabricated spacer. The infection eradication rates were 93% and 78% ($p>0.05$) for patients treated with a functional articulating spacer and for patients treated with a prefabricated spacer respectively.

The mean duration of the first-stage procedure was not statistically different ($p=0.14$), and neither was the second-stage procedure ($p=0.13$), for the functional articulating and prefabricated groups respectively. The duration of time patients were admitted to the hospital was significantly shorter for the patients with a functional articulating spacer, both after first-stage surgery ($p<0.01$), as well as after the second-stage procedure ($p<0.01$).

The number of patients with a spacer dislocation was not significantly different for the functional articulating or prefabricated spacer group ($p>0.05$). However, the number of dislocations per patient experiencing a dislocation was significantly higher for patients with a prefabricated spacer ($p<0.01$). Revision of the spacer due to recurrent dislocations was performed more often in the prefabricated spacer group, without reaching significance ($p=0.15$).

Failure patients

We considered thirteen patients as failure of treatment after two-stage revision of the hip. Mean age of these patients was sixty-seven years (range 50-88 years) at first-stage surgery. There were ten females and three males. Mean Body Mass Index (BMI) was 32 (range 24-37). Seven patients were American Society of Anesthesiologists score (ASA) 3, the other six were ASA 2. Five patients had died at final follow-up, all of these patients had ASA 3. The eight patients who were alive at follow-up completed the HOOS, EQ-5D and EQ-VAS questionnaires and scored mean 20 (range 5-39), 0.1486 (range -0.128-0.693) and 52 (range 30-80) respectively. None of the patients reached PASS for any of these outcomes. Two of these seven patients received lifelong suppressive antibiotic therapy, the others had a Girdlestone situation.

DISCUSSION

This study compared patient reported outcome, infection eradication rate and complications for functional articulating spacers and prefabricated spacers used in two-staged revision arthroplasty for PJI of the hip. Infection eradication rate seemed higher for patients treated with a functional articulating spacer than for patients treated with a prefabricated spacer (93% versus 78% respectively). Both these infection eradication rates are in concordance with the literature.[10, 11]

The patients treated with a functional articulating spacer achieved patient reported outcome scores above or close to the PASS, reflecting an acceptable state of functioning from a patient's perspective as described by Paulsen, whereas the patients treated with a prefabricated spacer achieve much lower scores.[14] The results of the HOOS, EQ-5D and EQ-QoL show patients treated with a functional articulating spacer achieved significantly higher scores compared to the patients treated with a prefabricated spacer. The difference may be partially explained by heterogeneity of the two patient groups, however correcting for age and comorbidity made no difference. We think these higher scores adequately reflect the better functional recovery of patients with a functional spacer, which has large implications for long-term quality of life.

As expected, patients with a Girdlestone situation scored lowest of all groups on the HOOS and the EQ-5D. The impact of permanent explantation of the hip prosthesis on patients' lives may be reflected even better with the EQ-QoL score, where patients with a Girdlestone situation score only a median 40 of a possible 100. Orthopaedic surgeons should be aware of this very poor functional outcome and decreased quality of life when counselling and preparing their patients for explantation of a hip prosthesis.

Patients treated with a functional articulating spacer had significantly shorter in-hospital stay after both first-stage and second-stage surgery. This effect may be biased by the year of surgery, as patients treated with a functional articulating spacer were treated more recently compared to patients treated with a prefabricated spacer. In recent years there has been increased emphasis on a shorter in-patient period, both after primary and revision arthroplasty.[16, 17] However, with a functional articulating spacer the patients' mobility is improved and patients can therefore go home more often and sooner and there is less need for discharge to rehabilitation clinics.

Duration of surgery was longer for the prefabricated spacer group during first stage surgery as well as during second stage surgery, without reaching significance. One could expect that spacer removal would be more difficult and time-consuming in patients with a functional articulating spacer, as these stems have been cemented in contrast to the prefabricated spacers. However, by maintaining normal motion with the functional articulating spacer, these patients may suffer less arthrofibrosis of the hip joint due to improved mobilization during the spacer interval, possibly resulting in an overall easier reimplantation procedure.

Spacer dislocation occurred in two out of fifteen patients with a functional articulating spacer and in ten out of fifty-five patients with a prefabricated spacer. Both patients with a functional articulating spacer had a single dislocation that was treated with a closed reduction. In patients treated with a prefabricated spacer dislocation reoccurred twenty-five times in ten patients. Spacer revision because of repetitive dislocations was performed in seven patients with a prefabricated spacer. The higher dislocation rate in patients with a prefabricated spacer can be explained by the limited number of modifications that can be made to prefabricated spacers, possibly resulting in less soft-tissue balance around the spacer and thus a higher risk of dislocation. Gil Gonzalez and colleagues have tried to prevent dislocation by proximal cementation of the prefabricated spacer, but this did not result in significantly less dislocations in their patient series.[18]

This study has several limitations which impede drawing definite conclusions. A weak point of this study is reflected by the retrospective design. There were no baseline PROMs available to compare to the PROMs at follow-up, therefore we cannot exclude that the groups had different baseline scores. The number of patients included in this study is low, which is caused by the relative scarcity of PJI requiring two-stage revision. Due to the long period of time in which patients were treated, differences in outcome may partially rely on other smaller changes in treatment that may have occurred over that interval of time. The heterogeneity of the two groups can cause bias in favor of the functional articulating spacer group, as patients in this group are slightly younger, less patients have an ASA classification >2, there is a difference in causative pathogens between the groups and follow-up is shorter compared to patients in the prefabricated spacer group (Table 1). These differences were not caused by patient selection, since initially all patients were treated with a prefabricated spacer and later all patients with a functional articulating one. Duration of in-hospital stay may also be influenced by the year patients were treated, as in recent years the emphasis on short term in-hospital stay has become stronger. Longer follow-up should determine whether the improved outcome of the functional articulating spacer group lasts.

Two-stage revision arthroplasty is a physically demanding procedure to endure, especially for frail elderly patients. Although this was not investigated in our cohort, in cases where the spacer is well-fixed, the use of a functional articulating spacer may even facilitate withholding a second stage procedure in high-risk and low-demand patients. Several studies have described patients refusing further procedures because they were satisfied with the function of the spacer.[4] Long-term results of retained functional articulating spacers have yet to be studied.

This was the first study to compare patient reported outcomes between groups of patients treated with two-stage revision arthroplasty for infection of the hip with a functional articulating or prefabricated spacer. Functional articulating spacers seem to lead to significantly improved patient reported functional outcome, reaching a functional status that is acceptable to patients; comparable or even better infection eradication rate and less perioperative complications, after two-stage revision arthroplasty of an infected total hip prosthesis, compared to prefabricated antibiotic-loaded spacers. The authors believe that, if technically possible, all two-stage revision procedures of the hip should be performed with the use of a functional articulating spacer, as this study shows clear advantages for this type of spacer. There is a need for a prospective randomised controlled trial studying the infection eradication rate and

functional outcome of patients during the spacer interval and at long-term follow-up. As randomised trials are difficult to organise due to the low percentage of infections, performing this study as a cluster randomised controlled trial should be executable.

Failure of two-stage revision and subsequent explantation of the prosthesis leads to very poor quality of life. Whenever possible, patients should be counseled about this outcome.

AUTHOR CONTRIBUTIONS

All authors were responsible for the design of the study and drafting and/or revising the manuscript. Data selection and statistical analysis were performed by ESV.

DECLARATION OF COMPETING INTERESTS

The Authors declare that there is no conflict of interest.

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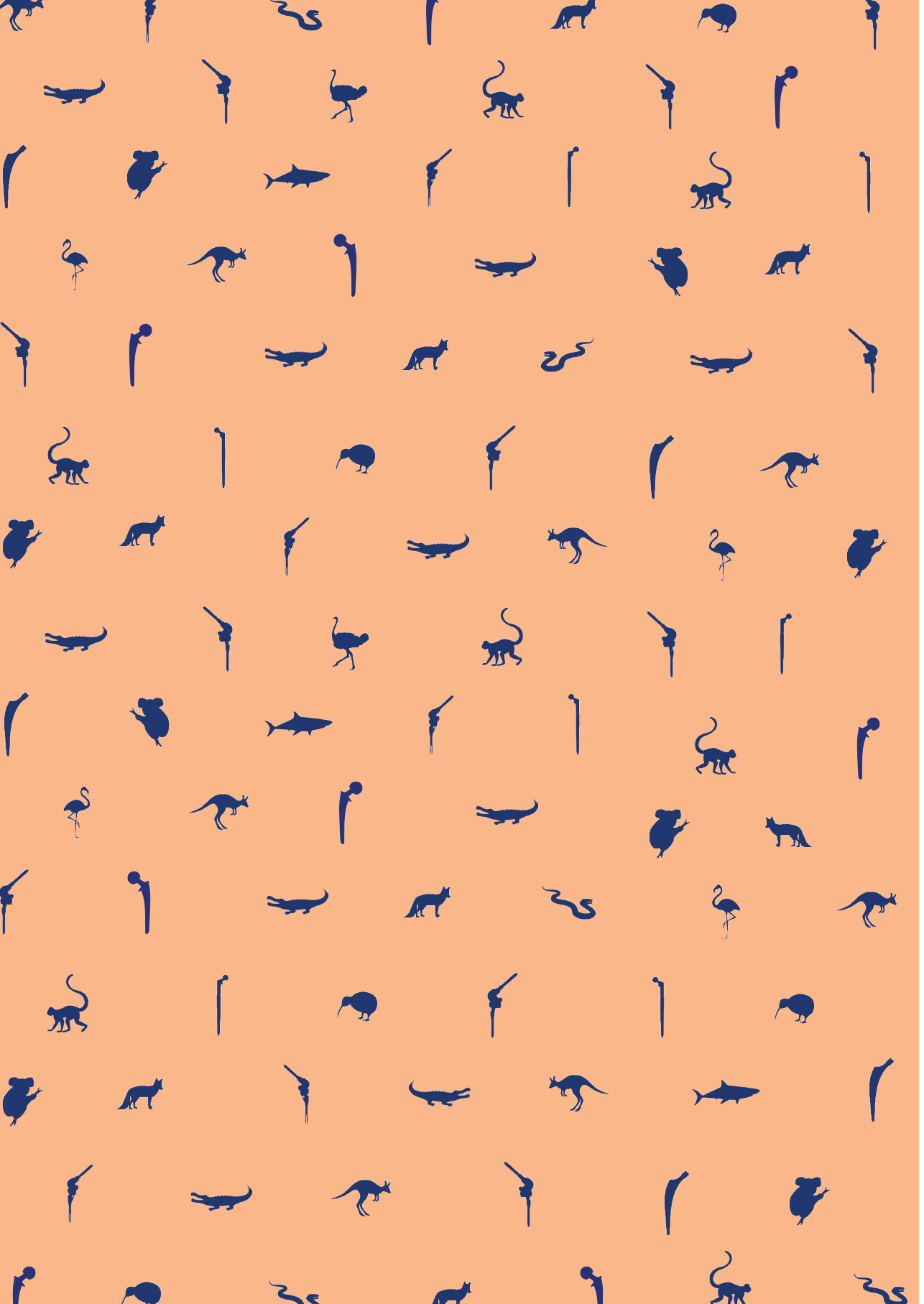
SECTION

4



CHAPTER

8

Two-Stage Revision Arthroplasty for Coagulase-Negative Staphylococcal Periprosthetic Joint Infection of the Hip and Knee

(World Journal of Orthopedics. 2019; 10(10): 348-355)

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ABSTRACT

Background Periprosthetic joint infections (PJIs) are frequently caused by coagulase-negative Staphylococci (CoNS), which is known to be a hard-to-treat microorganism. Antibiotic resistance among causative pathogens of PJI is increasing. Two-stage revision is the favoured treatment for chronic CoNS infection of a hip or knee prosthesis. We hypothesised that the infection eradication rate of our treatment protocol for two-stage revision surgery for CoNS PJI of the hip and knee would be comparable to eradication rates described in the literature.

Aim All patients treated with two-stage revision of a hip or knee prosthesis were retrospectively included. Patients with CoNS infection were included in the study, including polymicrobial cases. Primary outcome was infection eradication at final follow-up.

Methods Forty-four patients were included in the study. Twenty-nine patients were treated for PJI of the hip and fifteen for PJI of the knee. At final follow-up after a mean of 37 mo, recurrent or persistent infection was present in eleven patients.

Results Forty-four patients were included in the study. Twenty-nine patients were treated for PJI of the hip and fifteen for PJI of the knee. At final follow-up after mean thirty-seven months recurrent or persistent infection was present in eleven patients.

Conclusion PJI with CoNS can be a difficult to treat infection due to increasing antibiotic resistance. Infection eradication rate of 70%-80% may be achieved.

Keywords: Periprosthetic joint infection; two-stage revision; knee arthroplasty; hip arthroplasty; coagulase-negative Staphylococcus.

INTRODUCTION

Coagulase negative staphylococci (CoNS) are known to be a hard-to-treat group of micro-organisms in relation to implanted foreign materials, due to a high rate of methicillin resistance and the biofilm formation.[1] In recent years the incidence of infections with CoNS has increased.[2, 3] Periprosthetic joint infection (PJI) is a devastating complication after hip and knee arthroplasty and occurs in 1-2% of patients.[4] When infection persists despite debridement procedures or when infection is diagnosed more than three months postoperatively it is considered a chronic infection.[5] In case of chronic PJI removal of the prosthesis is usually indicated.[6] Two-stage revision arthroplasty with the use of an antibiotic loaded spacer is the gold standard treatment in case of persisting or chronic infection.[7, 8]

The type of spacer used during two-stage revision does not influence the infection eradication rate.[9, 10] In contrast, characteristics of the causative microorganism do influence the chance of infection eradication after two-stage revision.[11] Resistance to commonly prescribed antibiotics is an increasing problem as well.[11] Bacteria such as CoNS can form a biofilm on the prosthesis that prevents elimination by host defenses and antimicrobial therapy.[1, 12] In orthopaedic revision arthroplasty the rate of resistance to antibiotics by CoNS is increasing.[13] The effects of infection exclusively by CoNS on the outcome after two-stage revision arthroplasty have not yet been described.

The objective of this study was to evaluate infection eradication rate after two-stage revision arthroplasty of the hip and knee in patients with CoNS periprosthetic joint infection.

PATIENTS AND METHODS

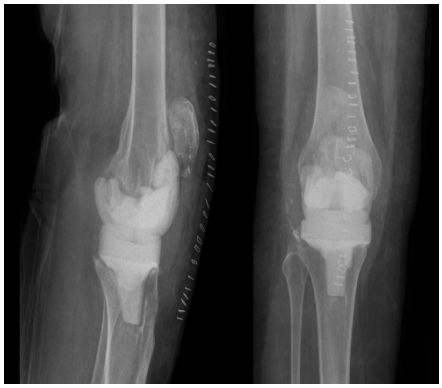
We used the STROBE cohort checklist when writing our report.[14] This study was approved by the local medical ethics committee. After approval, we retrospectively reviewed the records of all patients who had two-stage revision arthroplasty of the hip or knee in our hospital between 2003 and 2016. We included all patients with CoNS periprosthetic joint infection of the hip or knee in the study. Exclusion criteria were monomicrobial infection with bacteria other than CoNS and patients receiving a one-stage revision. Patients with polymicrobial infection, in which CoNS was one of the infecting organisms, were included in the study. In all patients diagnosis of infection was affirmed according to the MSIS criteria. Joint aspirations were routinely performed preoperatively and were positive in all patients.

During first-stage surgery we removed the infected prosthesis including all bone cement (when present). Multiple tissue samples were taken for culture, after which we

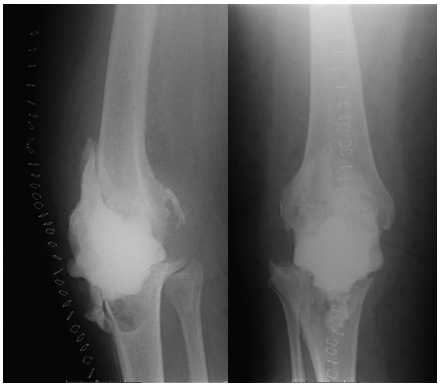
administered cefuroxime antibiotic prophylaxis. We did not perform sonication of the removed prosthesis. After meticulous debridement, we implanted an antibiotic-loaded interval spacer with gentamicin and vancomycin. In patients with an infected THA we used either a functional articulating spacer or a prefabricated cement spacer (figure 1A and B).[10] Functional articulating spacers consist of (parts of) regularly used hip arthroplasty components combined with antibiotic-impregnated cement. Prefabricated cement spacers are commercially available in different head sizes and two different lengths. In patients with an infected TKA we used either static spacers or dynamic spacers (figure 1 C and D).[15] Static spacers are blocks of antibiotic-loaded cement which are molded by hand intra-operatively. Patients were not allowed to bear weight on the static spacer and performing range of motion exercises was not possible. The dynamic spacers were either prefabricated cement blocks, or cement molded by hand in the shape of a knee prosthesis.

Figure 1

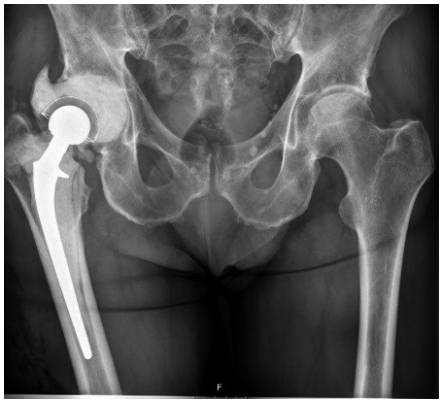
A. dynamic knee spacer



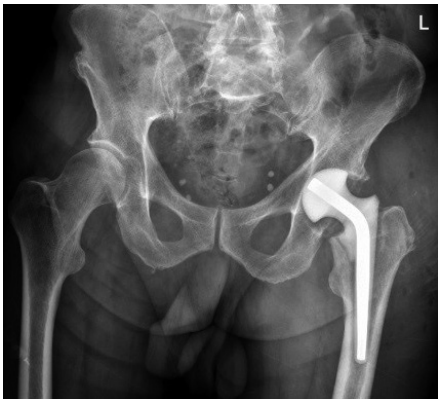
B. static knee spacer



C. Functional hip spacer



D. prefab hip spacer



We treated patients with antibiotics according to the recommendations as published by Zimmerli and colleagues.[4] Patients received intravenous antibiotics for at least two weeks based on the antibiogram of the cultured bacteria. Whenever possible, after two weeks we switched antibiotics to an oral substitute for an additional 4 weeks minimum. The exact antibiotic treatment was determined in close consultation with a microbiologist and an infectious disease specialist. Two weeks before the second stage procedure we discontinued antibiotics to achieve a two-week antibiotic free interval.

During second stage surgery we extracted the antibiotic loaded spacer. Again we took multiple tissue samples for culture, after which we administered antibiotic prophylaxis. We adjusted the postoperative antibiotic prophylaxis for the antibiogram of the bacteria cultured after the first stage procedure. We performed another thorough debridement, after which we implanted a revision prosthesis. Postoperatively patients received intravenous cefuroxime until culture results were available after two weeks. When culture results were negative, we ceased antibiotics and patients were discharged. In case cultures were still positive, we continued antibiotics for a total of 12 weeks.

We retrieved general patient characteristics, pre- and postoperative lab results, complications during treatment and final outcome from patients' records. Primary outcome was infection eradication after second-stage procedure, which was defined as absence of clinical, radiological or laboratory signs of infection at the latest follow-up, with a minimum of one year after second stage surgery. Secondary outcomes were complications registered during the spacer period and at final follow-up.

Failure of treatment was defined as persisting or repeated infection after second stage procedure, making it necessary to perform another revision, resection arthroplasty, arthrodesis or amputation of the limb or use of suppressive antibiotics at final follow-up.[16] We used descriptive statistics, mean and range to represent the demographics of the patients. Excel and SPSS software were used to perform calculations and statistical analyses. We analyzed patients with two-stage revision of hip or knee as one group, as well as divided in groups according to the joint treated and the interval spacer used.

Funding

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RESULTS

Patient characteristics and general outcome

Between 2003 and 2016 we treated 44 patients with CoNS periprosthetic joint infection of a total hip or total knee prosthesis with two-stage revision arthroplasty using an antibiotic-loaded interval spacer. General patient characteristics can be found in table 1. Polymicrobial infection was present in 6 patients. Coagulase negative staphylococci were sensitive to flucloxacillin or clindamycin in 19 patients. Due to antibiotic resistance to flucloxacillin and clindamycin we treated 23 patients with vancomycin. We treated 2 patients with linezolid for 4 weeks.

Table 1: General patient characteristics

	Hip	Knee	Total
Number of patients	29	15	44
Mean age	66	64	66
Gender, female	15	11	26
Mean BMI	27	30	28
BMI >30 (patients)	8	9	17
Indication for primary prosthesis			
Osteoarthritis	19	15	34
Posttraumatic	10	0	10
Comorbidity			
Immune suppression	3	2	5
Previous PJI	2	5	7
Diabetes mellitus	5	3	8
Obesity (BMI>30)	8	9	17
Active smoking	7	4	11
ASA 1/2/3	1/18/10	1/11/3	2/29/13

BMI = Body Mass Index, PJI = Periprosthetic Joint Infection, ASA = American Society of Anaesthesiologist score

Laboratory results showed a mean C-reactive protein level (CRP) of 58 mg/L (range 2-195) before first stage surgery. During the spacer interval the CRP gradually decreased to a mean 17 mg/L (range 2-186) before second stage surgery. At final follow-up the CRP had normalized at a mean 8 mg/L (range 1-28). The leukocyte count remained within normal limits before first and second stage surgery and at final follow-up.

At the time of the final follow-up, 3 patients had died due to reasons unrelated to treatment. The mean follow-up period was 37 months (range 12-119 months, median

31 months). Recurrent infection was present in 11 patients (7 hips and 4 knees). 4 of these patients had persistent infection with CoNS, the others had a re-infection with other bacteria. In addition to the patients with persistent infection, we considered 2 more patients failure of treatment.

Two-stage revision total hip arthroplasty

We treated 29 patients with two-stage revision arthroplasty of an infected total hip prosthesis, for which we used 8 functional articulating spacers and 21 prefabricated spacers (Table 1). Polymicrobial infection was present in 4 patients. Additional causative micro-organisms were *Propionibacterum acnes* in 1 patient, *Pseudomonas aeruginosa* in 1 patient, *Pseudomonas aeruginosa and Enterococcus faecalis* in 1 patient and *haemolytic Streptococci group C* in 1 patient. The other 25 patients had a monomicrobial infection with CoNS.

The spacer interval was complicated by dislocation of the spacer in 4 out of 21 patients with a prefabricated spacer and in 1 out of 8 patients with a functional articulating spacer. We performed spacer revision because of dislocation in 2 patients with a prefabricated spacer. Closed reduction was performed in the other 2 patients with a prefabricated spacer and the patient with a functional articulating spacer. Because of persistent wound effusion we performed spacer revision within 2 weeks after first stage surgery in 4 patients with a prefabricated spacer. No spacer exchanges were performed after more than 2 weeks.

We performed second stage surgery a median of 8 weeks (range 2-15 weeks) after the first stage procedure. During revision surgery, an uncemented modular femoral revision stem was used in 17 patients and a dual mobility cup was used in 8 patients. All other components used were primary cemented or uncemented stems and cups (head diameter 32mm). Postoperatively 12 patients received antibiotic treatment during the first 2 weeks until culture results were negative. 4 patients received antibiotic treatment for 6 weeks, 5 patients received antibiotics for 12 weeks and 1 patient received antibiotics for 26 weeks. Patients who had resection arthroplasty of the hip received antibiotics during 6 weeks in 4 cases and during 12 weeks in the other patient. 2 patients received lifelong suppressive antibiotic therapy, the first due to persistent CoNS infection and the latter due to re-infection with another bacteria.

At final follow-up we treated 22 patients successfully and considered 7 patients as failures after a mean follow-up of 42 months (range 12-119, median 31 months). Of the

7 patients considered failure of treatment, 6 were treated with a prefabricated spacer. Due to persistent infection, we eventually accepted a Girdlestone situation in 5 patients. 2 patients received lifelong suppressive antibiotics.

Two-stage revision total knee arthroplasty

We treated 15 patients with two-stage revision arthroplasty of an infected knee prosthesis, using 4 static and 11 dynamic spacers (Table 1). Polymicrobial infection was present in 2 patients. The additional causative micro-organisms were *Enterobacter cloacae* in 1 patient and *Enterococcus faecalis* in 1 patient. The other 13 patients had a monomicrobial infection with CoNS.

Spacer interval was complicated by spacer exchange because of persistent wound effusion in 2 patients with a static spacer. In 1 patient with a dynamic spacer a quadriceps tendon rupture occurred peroperatively.

We performed second stage surgery a median of 8 weeks (range 4-27 weeks) after the first stage procedure. During second stage surgery a hinged type prosthesis was implanted in 11 patients, a constrained prosthesis in 2 patients and a primary prosthesis in 2 patients. All knee prostheses were cemented. Postoperatively 8 patients received antibiotic treatment during the first 2 weeks until culture results were negative. 2 patients received antibiotic treatment for 6 weeks, 2 patients received antibiotics for 12 weeks and 1 patient received antibiotics for 26 weeks. 2 patients received lifelong suppressive antibiotic therapy, both due to persistent CoNS infection.

At final follow-up we treated 9 patients successfully and considered 6 patients as failures after a mean follow-up of 28 months (range 12-59, median 31 months). Due to persistent infection of the knee 2 patients treated with a static spacer underwent further surgical procedures. We performed a second two-stage revision procedure which eradicated the infection in 1 patient and an arthrodesis of the knee in the other patient. 2 patients treated with a dynamic spacer received lifelong suppressive antibiotics. We performed an above the knee amputation because of persistent pain in 1 patient who was treated with a static spacer and an arthrodesis of the knee because of insufficiency of the extension mechanism in 1 patient who was treated with a dynamic spacer. The latter 2 patients had no demonstrable infection during second stage, but they are considered as failure of treatment.

DISCUSSION

This study retrospectively evaluated the infection eradication rate after two-stage revision arthroplasty with the use of an antibiotic-loaded interval spacer of periprosthetic joint infections of the hip and knee caused by CoNS. At final follow-up infection was eradicated in thirty-three out of forty-four cases, however we considered two more cases as failure of treatment.

Poor rates of infection eradication have been reported in cases with polymicrobial infection of the hip or knee.[17] In our series out of six patients with polymicrobial infection in one patient treatment failed. Existence of polymicrobial infection did not seem to influence chance of infection eradication negatively, however the number of polymicrobial infections was too small to draw definite conclusions.

Infection eradication rate was comparable for two-stage revision of the hip (22 out of 29) and the knee (11 out of 15). The incidence of obesity (BMI over 30) was higher in the knee group compared to the hip group (8 out of 29 vs 9 out of 15 patients). Obesity is a known risk factor for PJI.[18-20] In this series of patients, obesity was not related to a higher risk of persistent infection after two-stage revision arthroplasty of the hip or knee. Recurrence of infection after two-stage revision arthroplasty was also not related to gender, age, smoking status or ASA-classification.

One third of patients (10 out of 29 patients) in the group of two-stage revisions of the hip had a primary hip prosthesis due to a proximal femoral fracture. In the Netherlands yearly four percent of total hip arthroplasties are implanted because of a femoral neck fracture.[21] This may imply that the risk of infection is higher in patients receiving a total hip arthroplasty after a femoral neck fracture. Physicians need to be aware of the increased risk of infection when providing information about hip arthroplasty to patients with hip fractures. Efforts should be made to optimally prepare the patient preoperatively. Treatment of comorbidities causing the trauma, timing and duration of surgery, perioperative antibiotic prophylaxis and soft tissue management may all influence the chance of periprosthetic infection after total hip prosthesis for a proximal femur fracture. Infection eradication rate after two-stage revision hip arthroplasty was similar in trauma and elective patients (respectively 7 out of 10 patients versus 14 out of 19 patients without infection at follow-up).

A weak point of this study is reflected by the retrospective design. The number of patients included in this study is relatively low, which is caused by the scarcity of

PJI requiring two-stage revision and the fact that in this study we only focused on CoNS infections. Treatment of patients treated before 2007 was more heterogeneous compared to patients treated after 2007 due to the implementation of stricter perioperative protocols concerning treatment of infected prostheses.

Current literature lacks high quality studies determining optimal treatment strategy in case of specific causative micro-organisms such as CoNS in periprosthetic joint infection of the hip and knee. As prospective studies of PJIs are hard to perform due to the scarcity of prosthetic infections, a retrospective multicenter study combining groups of patients to achieve a greater number of patients with CoNS PJI can provide more evidence on how to treat this specific infection. Orthopaedic surgeons should consider treating their patients with a functional articulating spacer of the hip or a dynamic spacer of the knee, as these may improve infection eradication rate. Whether or not functional outcome after two-stage revision with a functional articulating spacer of the hip or a dynamic spacer of the knee is improved compared to their more static counterparts has yet to be studied.

Due to biofilm formation CoNS can be a difficult to treat organism in periprosthetic joint infections. The results of this study show that infection eradication rate comparable to that of other causative pathogens may be achieved following two-stage revision arthroplasty of the hip and knee.[22-24]

CONTRIBUTION OF AUTHORS

ESV was responsible for study design, extraction and interpretation of data, and draft of the manuscript. DJM, MvO and RWP were responsible for study design, draft and/or revision of the manuscript.

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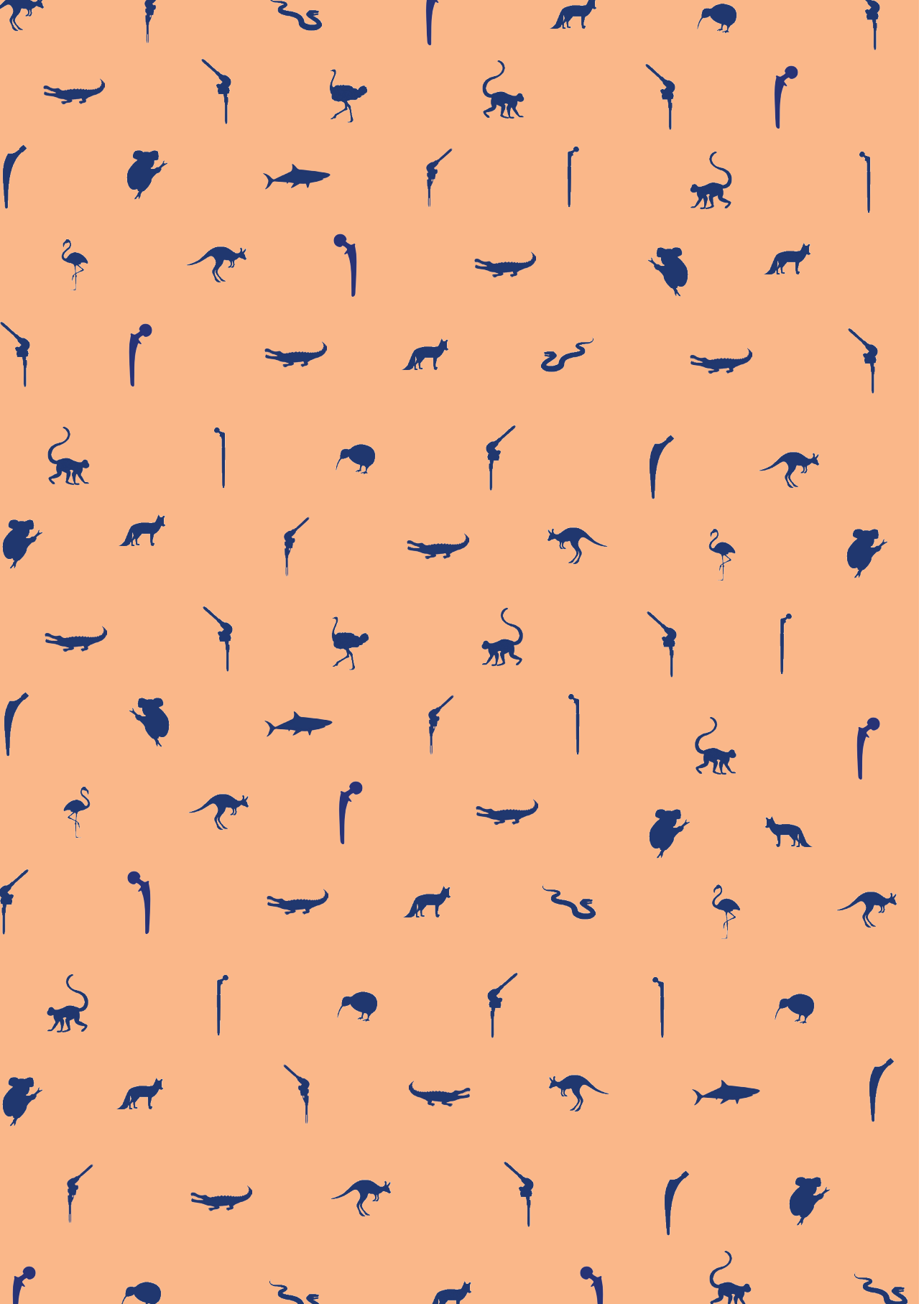

CHAPTER

9

Revisions for culture-negative total knee arthroplasties, a case-control clinical evaluation of functional and patient reported outcome of two-stage revision versus one-stage revision

(submitted)

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ABSTRACT

Background Diagnosis of periprosthetic joint infections can be troublesome due to the low sensitivity of diagnostic tools. In case of infection a two-stage revision of a knee prosthesis is merited, while in aseptic cases one-stage revision provides a less strenuous treatment option. The differences in outcome between two-stage and one-stage surgery for aseptic cases have only scarcely been described.

Methods We selected all patients who underwent two-stage revision surgery, but that did not meet the infection criteria in retrospect. These patients were compared to a matched cohort of patients who underwent one-stage revision. Patients were matched using patient characteristics and reason for revision. Patient reported outcome measures (PROMs), knee function and complications of treatment were the outcomes.

Results We included twenty-three patients in the two-stage group and matched these to patients in the one-stage group. At final follow-up after mean thirty-eight months patients in the one-stage group achieved significantly better scores on the KOOS pain and symptom subscales, and slightly improved mean range of motion. Three patients in the two-stage group acquired an infection in between stages.

Discussion In the absence of a positive preoperative work-up for infection, orthopaedic surgeons should adhere strictly to the infection criteria when determining treatment strategies for patients they clinically suspect of infection, as two-stage revision surgery seems to lead to moderately impaired outcomes and increased risk of complications compared to one-stage revision in non-infected patients.

Keywords: two-stage revision; one-stage revision; knee arthroplasty; patient reported outcome.

INTRODUCTION

About one in every eight patients reports unsatisfactory results after total knee arthroplasty.[1,2] Aseptic loosening, prosthetic joint infection (PJI), malalignment, overstuffing, arthrofibrosis, fracture or fissure, and malrotation of prosthetic components are some of the many factors recognized as causes for persisting complaints after primary total knee arthroplasty.[1,2] The optimal type of treatment varies markedly for the different causes of persisting pain, therefore the importance of having the correct diagnosis before the initiation of treatment is eminent.

The Musculoskeletal Infection Society (MSIS), the Infectious Diseases Society of America (IDSA), the European Bone and Joint Infection Society (EBJIS) and the International Consensus Meeting have proposed criteria which can be used to qualify a patient as suspected for PJI or not.[4-6] Positive cultures of periarticular fluid or tissue, and the presence of a sinus tract around the prosthesis are considered to be major criteria and pathognomonic for PJI.[7] The presence of three minor criteria would also confirm the diagnosis of infection. Minor criteria are elevated serum CRP and ESR, elevated synovial white blood cell count, elevated polymorphonuclear neutrophil percentage or positive change on the leukocyte esterase test strip or alfa-defensin, positive histological analysis of periprosthetic tissue and a single positive culture.[7] Thus cornerstone of infection diagnosis, in absence of a sinus tract, remains a positive synovial fluid culture.[4] However, even with prolonged incubation of cultures a vast part of cultures remain negative.

The sensitivity of synovial fluid cultures for the detection of a periprosthetic joint infection (PJI) is low, making it impossible to definitely exclude infection as a cause of pain or loosening after primary knee arthroplasty only based on a negative culture result.[8,9] The percentage of culture-negative infection cases in published cohort studies is reported up to 22% of included cases, which is exemplary for this diagnostic dilemma.[10] Missing the diagnosis of infection may lead to under-treatment and subsequent worse outcome for the patient.[11] That is why many authors advocate treating patients suspected of infection but with negative cultures as aggressively as their culture-positive counterparts.[10,12-14] The diagnostic insecurities frequently lead to doubt about the optimal type of treatment in patients that preoperatively do not fully meet the infection criteria, for example patients with early postoperative loosening or with peroperative indistinct joint fluid, and can lead to subsequent two-stage treatment of non-infected patients. Probably, many patients are subjected to more rigorous treatment methods than would have been required, because of this diagnostic dilemma.

On a daily basis, orthopaedic surgeons who perform revision knee arthroplasties have to make decisions balancing on the delicate equilibrium between optimal treatment in case of infection versus less invasive treatment in case of a non-infected patient. As many orthopaedic surgeons are reluctant to expose their patients to the risk of under-treatment of infection, patients may be subjected to over-treatment by performing a two-stage revision where a one-stage revision would have been sufficient.

The aim of this matched-pair analysis is to determine whether patients, who retrospectively did not meet the infection criteria, achieve different patient reported outcome, functional outcome and complications after two-stage revision compared to patients with aseptic causes who received a one-stage revision. We hypothesize that patients who are treated with a two-stage revision, achieve worse patient reported and functional outcome compared to patients treated with a one-stage revision.

METHODS

We used the STROBE cohort checklist when writing our report.[15] This clinical evaluation study was approved by the local medical ethics committee, with number 15.080. Sample size calculation (with expected mean improvement of PROMS of 10% for the one-stage group, enrollment 1:1, alpha of 0.05 and 80% power) showed that at least 16 patients per group should be included.

After approval, we retrospectively reviewed the records of all patients who had two-stage revision knee arthroplasty between 2004 and 2016 and compared these to the infection criteria as postulated by Osmon and colleagues and Parvizi and colleagues in 2014.[4,6] All patients were assessed according to these criteria and cultures taken preoperatively and at first-stage surgery were evaluated. The reason for revision in the two-stage group was re-classified using chart data from the preoperative outpatient clinic evaluation (table 1). We then selected control cases from a cohort of patients treated with one-stage revision of a knee prosthesis for aseptic reasons, and matched the groups on patient characteristics (age, gender, BMI, comorbidity, ASA classification score, smoking status) and reason for revision. These patients were included in the one-stage (OS) group.

For both groups, during first-stage surgery we removed the infected prosthesis including all bone cement. Multiple tissue samples (at least four) were taken for culture, after which we administered cefuroxime antibiotic prophylaxis. After meticulous debridement, we implanted an antibiotic-loaded interval spacer with gentamicin

and vancomycin in the TS group and a (revision) knee prosthesis in the OS group. Postoperatively patients in the TS group were treated with cefuroxime until the definite culture results of first-stage surgery were available after two weeks. Patients in the OS group were prophylactically treated with cefuroxime for one to five days.

We retrieved general patient characteristics, complications during treatment, functional results and final outcome from patients' records. Patients were contacted to complete the patient reported outcome measures. At final follow-up, the Knee Osteoarthritis Outcome Score (KOOS) (range of scores 0-100, with 100 as the optimal score) with its subscores for pain, symptoms, activities of daily living (ADL), sports and quality of life (QoL), and the EQ-5D questionnaire (range of scores -.500 to 1.00, with 1.00 as the optimal score) and the EQ-5D QoL thermometer (range of scores 0-100, with 100 as the optimal score) were used to assess patient reported outcome.[12,13]

Primary outcomes were infection eradication and patient related outcome scores after revision surgery. Secondary outcomes were functional outcome and complications reported during the spacer period and at final follow-up. Patients were analyzed for the type of revision procedure they were treated with. Descriptive statistics, mean and range are used to represent the demographics of the patients. For numerical data t-test was used and for categorical data Chi-squared tests was used to assess the level of significance for differences between the groups, a p-value <0,05 was considered to be statistically significant. Calculations and statistical analyses were performed using Excel and SPSS software.

RESULTS

We identified twenty-three patients that were treated with a two-stage revision arthroplasty of the knee between 2004 and 2016, and who did not meet the PJI criteria preoperatively and had negative preoperative joint aspirate and negative peroperative tissue cultures at first stage. These patients were included in the two-stage (TS) group. In these patients suspicion of infection was mainly present due to early postoperative loosening of the prosthesis, persistent pain or repetitive swelling of the joint. The reason for revision was retrospectively re-classified using chart data from the preoperative outpatient clinic evaluation (table 1). We then matched these patients to twenty-three patients treated with one-stage revision of a knee prosthesis for aseptic reasons. These patients were included in the one-stage (OS) group. General patient characteristics, infection characteristics and reasons for revision are listed in table 1. There were no statistically significant differences between the groups.

Two-stage vs. One-stage

Peroperative cultures of first stage surgery were negative in all 46 patients (table 1). The complications, range of motion at follow-up, KOOS and EQ-5D scores, and statistical analysis of the outcomes are displayed in table 2.

Table 1: Patient characteristics, infection characteristics and reason for revision

	Two-stage group	One-stage group	p
Patient characteristics			
Number of patients	23	23	N.S.
Age (range)	66 (58-76)	68 (54-78)	N.S.
Gender female	16	18	N.S.
BMI (range)	28 (20-35)	30 (22-42)	N.S.
BMI > 30	8	9	N.S.
Diabetes	3	3	N.S.
Active smoker	5	6	N.S.
ASA 1/2/3	5 / 14 / 4	4 / 14 / 5	N.S.
Preoperative flexion (range)	103 (45-140)	100 (80-130)	N.S.
Preoperative extension (range)	-4 (-25 – 5)	4 (-5 – 35)	N.S.
Months from primary surgery (range)	33 (12-96)	48 (12-132)	N.S.
Months follow-up (range)	46 (12-120)	37 (12-62)	N.S.
Infection characteristics			
Soft tissue involvement	0	0	N.S.
Mean preoperative CRP (range)	6 (1-26)	4 (1-28)	N.S.
Mean preoperative Leukocytes (range)	8 (5-13)	7.4 (4-13)	N.S.
Preoperative culture neg/pos	23/0	23/0	N.S.
Peroperative cultures neg/pos	23/0	23/0	N.S.
Reason for revision			
Aseptic loosening	11	11	N.S.
Persisting pain/restricted ROM	10	10	N.S.
Component malrotation	2	2	N.S.

N.S. = Not significant. BMI = Body mass index. ASA = American Society of Anesthesiologists score.

The spacer interval in the TS group was a mean five weeks (range 2-8). Three patients in this group had (two or more) positive cultures at second-stage reimplantation, with a coagulase-negative Staphylococcus in two cases and a Streptococcus species in the latter case. All three infections were successfully treated with 3 months of antibiotics.

All other patients had negative cultures at second-stage surgery. In the OS group there were no infections.

Table 2: Follow-up results: score (range)

	Two-stage group	One-stage group	p
Complications			
Persisting pain	9	10	N.S.
Arthrofibrosis	3	0	N.S.
Infection	3	0	N.S.
ROM			
Flexion	102 (70-125)	108 (90-140)	N.S.
Extension	-1 (-10 - 0)	-1 (-10 – 5)	N.S.
KOOS			
Pain	55 (8-86)	68 (33-92)	0.03
Symptom	62 (32-86)	73 (39-93)	<0.01
ADL	53 (9-85)	62 (22-100)	N.S.
Sport	21 (0-69)	28 (0-70)	N.S.
QoL	40 (0-75)	50 (6-88)	N.S.
EQ-5D			
Score	0.540 (-0.259 - 1)	0.534 (-0.128 - 1)	N.S.
QoL	63 (40-80)	69 (40-80)	N.S.

ROM = range of motion. ADL = activities of daily life. QoL = quality of life.

The spacer interval in the TS group was a mean five weeks (range 2-8). Three patients in this group had (two or more) positive cultures at second-stage reimplantation, with a coagulase-negative Staphylococcus in two cases and a Streptococcus species in the latter case. All three infections were successfully treated with 3 months of antibiotics. All other patients had negative cultures at second-stage surgery. In the OS group there were no infections.

The number of patients with persistent pain was comparable in both groups. At final follow-up one patient in the TS group had an above-the-knee amputation because of persistent pain. There was no sign of infection at any stage before amputation. This patient did complete the EQ-5D, but logically not the KOOS. Three additional patients

underwent manipulation under anesthesia due to stiffness of the knee. No patients' knees were manipulated under anesthesia in the OS group.

The knee flexion was slightly, but not significantly, better in the OS group with a mean 108 (range 90-140) versus 102 (range 70-125) degrees respectively (p>0,05).

For the patient reported outcomes, one-stage patients scored significantly better on the Pain and Symptom subscores of the KOOS (table 2). On all other KOOS subscores and the EQ-5D scores the one-stage patients had better scores as well, but not significantly.

DISCUSSION

Our retrospective clinical evaluation shows that patients in the OS group achieved slightly more improvement in range of motion and significantly better scores for pain and symptoms, without reaching statistical significance for the other subscores of the KOOS and EQ-5D.

Three patients on the TS group had positive cultures at second-stage surgery, while cultures at first-stage surgery were negative. Probably, the causative pathogens were introduced perioperatively during first-stage surgery. All three patients were treated with antibiotics for three months, no further operative procedures were performed to treat the infection. We found no infectious complications in the OS group.

Persistent pain at follow-up was present in a comparable number of patients in both groups. Pain was the reason for revision in seven out of the nineteen patients with persisting pain postoperatively (four in the TS group and three in the OS group). Pain as reason for revision did not predict persisting pain postoperatively in this study.

Several studies have been performed comparing patients with culture-negative and culture-positive PJI. Li and colleagues have compared a group of culture negative patients treated with two-stage revision surgery to two groups of patients with positive cultures that were treated with one- or two-stage revision surgery.[12] They found similar outcomes at follow-up and, surprisingly, a similar chance of reinfection for both the infected and the non-infected patients. Patient reported outcome was not reported. Wang and colleagues, Santoso and colleagues and Reisener and colleagues all report comparable results of two-stage revision surgery for culture-negative and culture-positive patients.[13,14,17] Furthermore, Konrads and colleagues report comparable outcome in their group of patients treated with one-stage revision for aseptic reasons

compared to patients treated with two-stage revision surgery for PJI.[18] A group of patients that retrospectively did not meet the infection criteria and that was treated with two-stage revision surgery, has not been described before.

This study has several limitations. Selection bias can exist because of the retrospective design of this study. The number of patients included in this study is small, which is caused by the scarcity of two-stage revisions performed in patients with a low suspicion of infection in this single center study. PROM results are only available at follow-up, so a comparison of the preoperative PROM results is not possible, this may lead to bias if one group actually had better preoperative scores. Since our clinical evaluation lacks an experimental design we cannot draw causal conclusions.

For future studies, authors should aim at combining groups of patients from multiple centers to achieve a greater sample size. Results of such multicenter studies could greatly improve the power of studies and our understanding of the optimal treatment for patient with suspected periprosthetic joint infection.

To summarize, this study suggests that aseptic patients undergoing revision surgery seem to have a greater risk of poor outcome when treated with a two-stage procedure. Next to this, the extra procedure in case of two-stage surgery imposes a burden to the patient, hospital resources and healthcare system expenses. Obtaining the correct preoperative diagnosis is therefore essential for the patient, their treating orthopaedic surgeon and the healthcare system in general. Recently, the infection criteria have been adjusted and validated to improve the specificity and sensitivity. It has yet to be studied whether these findings are reproducible in larger sample sizes using experimental study designs.[19] Despite the urge not to miss any infections, orthopaedic surgeons should be wary to overtreat their patients as this may lead to unnecessary costs for the healthcare system and worse outcome for their patients.

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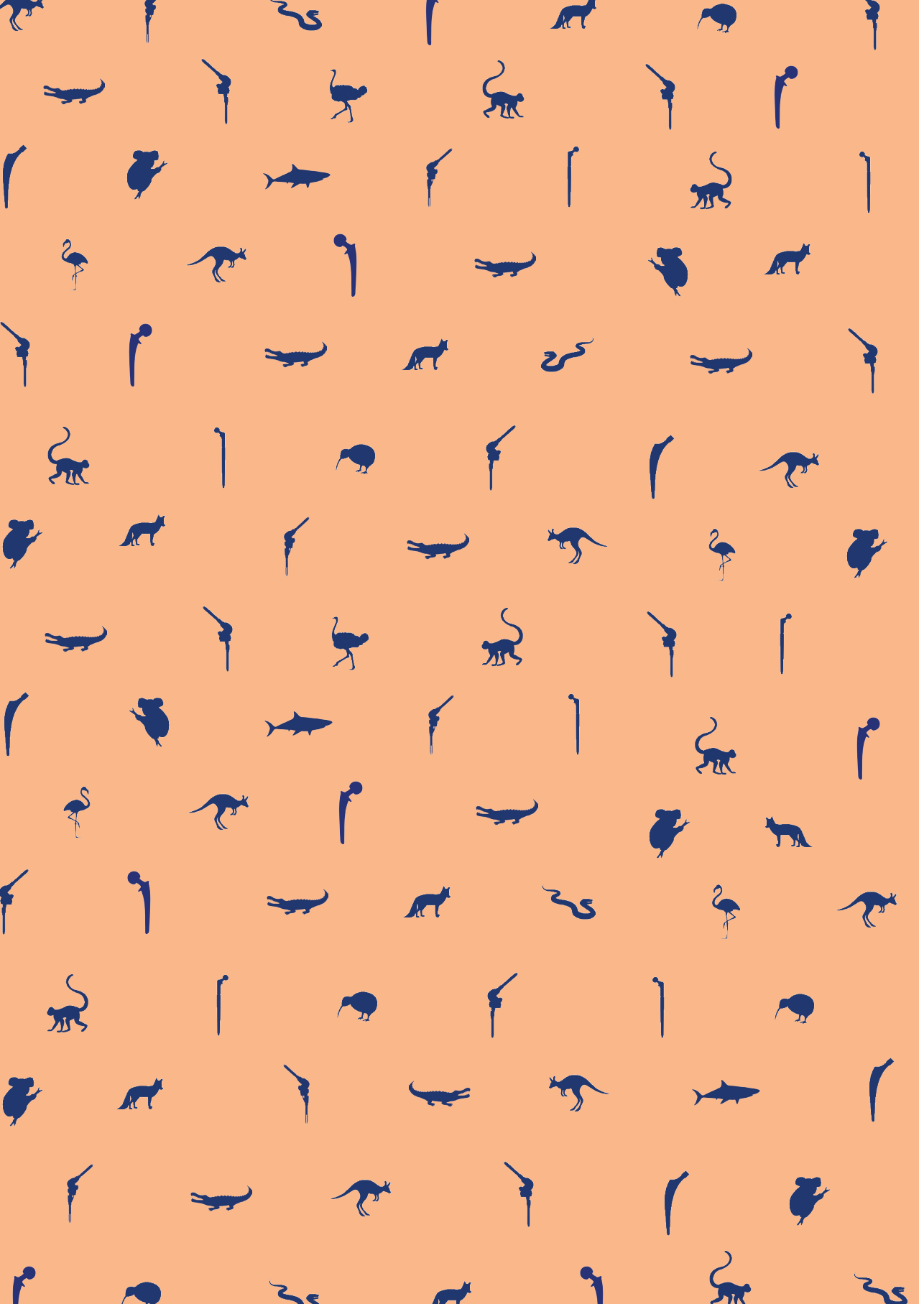

CHAPTER

10

Summary and General Discussion

SUMMARY AND AIMS OF THE THESIS

The work presented in this thesis aims to further evaluate strategies which can be used to prevent periprosthetic joint infection (PJI) after primary total hip or knee arthroplasty on the one hand, and to provide some evidence on treatment options for patients with a PJI. We have divided the thesis into sections to answer the questions formulated at the beginning of this thesis and described in the introduction.

KEY FINDINGS

Section 1: Prevention of Periprosthetic Joint Infection

Chapter two was a national survey performed in the Netherlands to evaluate the antibiotic prophylaxis regimens which are used in the Netherlands, to evaluate how treatment protocols for early infection of a hip or knee prosthesis were constructed and to evaluate the tendency of orthopaedic surgeons to register the DAIR procedures in the national joint registry LROI. The survey led to several findings:

All hospitals in the Netherlands adhered to the recommendations of the Netherlands Orthopaedic Society, to use a cephalosporin as antibiotic prophylaxis for primary hip and knee arthroplasty and to discontinue the administration of prophylactic antibiotics within 24 hours. Ninety percent of hospitals administered a multiple dose antibiotic prophylaxis of either cefazolin or cefuroxime, and ten percent of hospitals administered only one preoperative dose of cefazolin.

Currently, approximately 20% of hospitals do not to exchange the modular parts during DAIR procedures for treatment of early infection after hip or knee arthroplasty, which is in contrast with the recommendations of national and international societies on PJI treatment. Even though it is mandatory, registration of DAIR procedures of the hip and the knee in the LROI is only performed by 64% of the respondents. As a consequence, there is a serious underreporting of DAIR procedures in the LROI database, which therefore underestimates the number of infections after primary arthroplasty of the hip and the knee.

Next, parts of the aforementioned findings were combined with data on revision for infection after primary arthroplasty of the hip and knee within one year after primary surgery, to discover whether the antibiotic prophylaxis regimen on hospital-level had influence on the risk of infection within one year (**chapter three**). During 2011 to 2015, 130,712 primary total hip arthroplasties and 111,467 primary total knee arthroplasties were performed across 99 centers, information of all of these patients on hospital-level

was available for analysis. This study reports that there was a comparable risk of revision for PJI between the antibiotic prophylaxis regimens in terms of type of antibiotic and duration of prophylaxis during the first 12 months following surgery. The highest risk of revision for PJI in the year following the index surgery occurs within the first three months after the operation. After this period, the rate of treatment for PJI (defined as exchange of one or more components) rises again towards the end of the follow up period. The latter may indicate treatment for low-grade PJI infections.

In summary, **section one** of this thesis found that two specific protocols for duration of antibiotic prophylaxis are used for patients around primary arthroplasty of the hip and knee in the Netherlands. Furthermore, based on data from the Dutch Arthroplasty Register there seems to be no difference in risk of revision for infection within one year after surgery for any of these antibiotic prophylaxis regimens.

Section 2: Proceedings of International Consensus on Orthopedic Infections

Chapters four and five describe the results of the International Consensus Meeting (ICM) on Orthopedic Infections, which was held in 2018 in Philadelphia. The ICM is a collaborative initiative of, among others, the MusculoSkeletal Infection Society and the European Bone and Joint Infection Society. Four hundred orthopaedic surgeons and affiliated infection specialists from 51 countries joined forces to achieve consensus on pre-arranged topics concerning orthopaedic infections. These chapters did not generate new evidence, but this joint effort provides an overview of the best available evidence and the consensus of a large group of participating orthopedic surgeons in the field.

In **chapter four** we describe the consensus result on the treatment algorithm for acute infections of the hip and knee. Strong consensus was agreed on all four discussed topics. Early postoperative infections and acute hematogenous infections should be treated with a DAIR procedure. In case of sepsis, patients should have an acute surgical reduction of bacteria, either by implant retention and extensive debridement or removal of components (if feasible for that specific patient), along with concurrent antimicrobial therapy even in case of an acute on chronic infection. In case of persistent wound leakage after 10-18 days (which is currently being evaluated in the LEAK study) days postoperatively, operative treatment may be indicated, including DAIR. It is unknown which type of treatment is optimal for bilaterally infected hip and knee prostheses.

Chapter five summarises the opinion at a consensus meeting on variables which are favorable for a good outcome after a two-stage exchange of an infected hip or knee prosthesis. Strong consensus was achieved on three questions and weak consensus was achieved on the second question. Optimal timing of the second stage procedure has yet to be determined, timing of this surgical procedure depends on clinical evaluation by the treating physician. Under strict conditions, after meticulous debridement, a stable cement mantle can be left in place to minimise the damage to the femoral bone stock. Surgeons should consider whether the potential benefits of cement extraction from the pelvis or difficult anatomical positions outweigh the potential risks of persistence of infection. There is no evidence that using non-antibiotic-impregnated allograft for management of bone defects during reimplantation increases the risk of recurrence of PJI.

Section 3: The Functional Articulating Antibiotic-Loaded Hip Spacer

In **chapters six and seven** we studied the patient reported and functional outcomes and infection eradication rate of functional articulating spacers of the hip.

To start, we performed a systematic review of the literature to compare various types of spacers which are used during two-stage revision arthroplasty of the infected hip (**chapter six**). We compared functional outcome, patient reported outcome, infection eradication rate and complications for treatment with either a functional articulating spacer, a prefabricated spacer and a custom made spacer. This study reports that the infection eradication rates (93%, 96% and 95% respectively) and patient reported outcome for the Harris Hip score (90, 81 and 83 points respectively) were comparable. Most complications are evenly distributed among the three groups, except for the number of spacer dislocations. The incidence of spacer dislocation is high in the prefabricated spacer group as compared to functional articulating spacer and the custom made spacer groups (13%, 4% and 3% respectively). Although this appears to be a large difference, significance levels could not be calculated, due to heterogeneity of the original data.

Secondly, in **chapter seven**, we studied patient reported outcomes, infection eradication rate and complication rate of functional articulating spacers compared to prefabricated spacers in two groups of consecutively treated PJI of hip patients. This study reports a significant difference in patient reported outcome (EQ-5D and HOOS), and number of dislocations all in favor of the functional articulating spacer group, while

maintaining a comparable infection eradication rate (93% for the functional articulating and 78% for the prefabricated spacer groups).

In summary, **section three** shows that patients who are treated with a functional articulating spacer of the hip achieve at least a similar infection eradication rate, while having a favorable functional outcome as reported on different patient reported outcome measures and a lower risk of complications after two-stage revision of an infected hip prosthesis.

Section 4: Treatment of Periprosthetic Joint Infection

The infection eradication rate and complications after treatment of periprosthetic joint infection of the hip and knee with a Coagulase-negative Staphylococcus (CoNS) are studied in **chapter eight**. In twenty-two out of twenty-nine hip (76%) patients and eleven out of fifteen knee (73%) patients the infection was eradicated after two-stage revision surgery and antibiotic treatment. For hip patients, the infection eradication rate was higher (88%) when a functional articulating hip spacer was used, compared to a prefabricated hip spacer (71%, p>0,05). For knee patients, the success rate of treatment was higher when a dynamic spacer (82%) was used compared to a static spacer (50%, p>0,05). In conclusion, two-stage revision arthroplasty of the hip and knee and antibiotic treatment for PJI with a biofilm forming CoNS gives comparable eradication rates as PJI with non-biofilm forming microorganisms.

In **chapter nine**, we studied a group of patients who were treated with two-stage revision surgery of the knee and initial antibiotics for suspected periprosthetic joint infection, but who retrospectively did not meet the infection criteria. We reclassified the reason of revision of these patients and compared them to a matched cohort of patients treated with one-stage revision surgery for aseptic loosening of the implant, with focus on functional and patient reported outcome. This study reports that comparable range of motion was achieved for both groups. One-stage treated patients scores significantly better on the pain and symptoms subscores of the KOOS and comparable to the two-stage treated patients on the other subscores. Three patients in the two-stage group acquired a PJI between stages which was successfully treated with 12 weeks of antibiotics.

General conclusions and future perspectives

The studies included in this thesis investigated and evaluated some strategies for the prevention and treatment of periprosthetic joint infections. We showed that

there seems to be no difference in rate of revision for infection within one year, when comparing single dose and multiple dose antibiotics for primary arthroplasty of the hip and knee. We hypothesize that functional articulating spacers of the hip lead to comparable infection eradication rate and to improved patient reported outcome and less complications for patients treated with two-stage revision arthroplasty of the infected hip prosthesis. And we hypothesize that two-stage revision surgery of the knee seems to lead to comparable patient reported and functional outcome, but higher risk of complications in cases who do not meet the infection criteria.

In **section one** we have provided an evaluation of the current antibiotic prophylaxis regimens which are used for primary arthroplasty of the hip and knee in the Netherlands. Consecutively, we have evaluated whether the type of administered antibiotic prophylaxis had an effect on the risk of complete revision for PJI within one year after arthroplasty. This study resembles a natural experiment, which is a strength of this study. Limitations of this study are related to the observational nature of the data. Although prospectively collected, causality cannot be determined from these observational data. To establish true causality, a superiority or non-inferiority randomized controlled trial is needed. Despite the fact that a randomized controlled trial studying the optimal duration of antibiotic prophylaxis around primary hip and knee arthroplasties is hard to perform due to the vast number of patients that would have to be included to achieve sufficient power, we believe that such a study should be performed. Power analysis shows that over 17,000 patients should be included per arm of the study. Nesting the study in a national arthroplasty register, or using (stepped wedge) cluster randomization should allow inclusion of large numbers of patients, especially if an (inter)national collaboration could be set up.

In **section three** we have studied the literature to evaluate the outcome of different types of antibiotic-loaded spacers of the hip and we have retrospectively compared two groups of patients treated with either a functional articulating spacer or a prefabricated spacer. Our studies lead to the hypothesis that functional articulating spacers of the hip can provide a similar or improved infection eradication rate compared to more static spacer types, with a superior patient reported outcome. The main limitation of the retrospective comparative study is the small number of patients that could be included. A prospective trial should be performed to definitively prove that functional articulating spacers of the hip are more safe, effective and cost-efficient than their prefabricated counterparts and Girdlestone intervals. Remarkably, in 11% of patients with a functional articulating spacer included in the systematic review, no second stage procedure was

performed. This high incidence was caused by patients refusing second stage surgery because they were satisfied with the functional result after first stage placement of the functional articulating spacer. Outcome measures and functional results such as walking distance and range of motion were not specifically reported for the group of patients refusing second stage surgery. There is a need for a large, prospective study evaluating patient satisfaction and functional outcome after two-stage revision hip arthroplasty comparing various kinds of antibiotic-loaded spacers comparing with non-antibiotic loaded spacer to prevent micro-organism resistance. Although such a study is almost impossible to perform due to logistic reasons. The subgroup of patients who have a well-functioning antibiotic loaded spacer should be studied to evaluate the possibility of retaining the spacer for a longer period. The latter could be a viable treatment option for frail elderly patients with PJI.

Additionally, it should be studied whether the same positive effect occurs for patients with an infected knee arthroplasty, for whom currently no functional articulating spacers are available. Keeping the periarticular soft tissues in motion with a more functional type of spacer may improve knee function, decrease stiffness after revision surgery and improve patient reported outcome both during the spacer treatment and for the long term after revision surgery. Possibly, it may also improve the infection eradication rate and decrease the re-infection rate after revision surgery, as the compromised soft tissues play an incremental role in the (re)occurrence of infection.

In **section four** we showed that two-stage revision surgery of the knee seems to lead to comparable patient reported and functional outcome, but higher risk of complications in cases who do not meet the infection criteria retrospectively. This should urge orthopaedic surgeons to strictly adhere to the infection criteria when determining a treatment plan for their patients.

In the absence of level one evidence, retrospective data may indicate possible associations between treatment protocols that have been used and the consecutive outcome for treated patients. Retrospective studies can formulate new hypothesis, which should then be studies prospectively. As for prospective studies, the number of patients that can be included in retrospective studies is key. With the low incidence of infection, it may lead to improved quality of reporting on treatment for periprosthetic joint infections when multiple centers combine their patient databases to evaluate and compare treatment strategies. To date, the number of large-scale multicenter retrospective cohort studies is low. It may well be worth the effort to join forces, as the

power of performed studies will greatly increase of the number of included patients can be improved. Especially in a small sized country like the Netherlands combining data of multiple centers should be executable.

Even though periprosthetic joint infections have been in the center of attention in recent years, many details of treatment have not yet been studied. It is of great importance that treatment strategies are developed and thoroughly evaluated to provide sufficient evidence to base treatment protocols on. Clinical protocols, based on clinical evidence, thus not only on consensus meetings or even worse personal experience, on the treatment of prosthetic joint infections will lead to a eradication of infected prosthetic joints, with outcome for patients as well as reduction of costs for the healthcare system.

As for new promising treatment options for PJI, in the future the focus will be on a multimodal treatment without implant removal (if well fixed in the bone). Some promising results are seen ex-vivo with induction heating, peptides as well as nano-coatings at implants.[1-5]

The work is far from finished, and studies with a high level of evidence on the prevention and treatment of periprosthetic joint infections are needed. The aim to reach perfection in this devastating disease for patients with an implant has no finish line, as with every piece of evidence new questions arise, which invokes new challenges for research.

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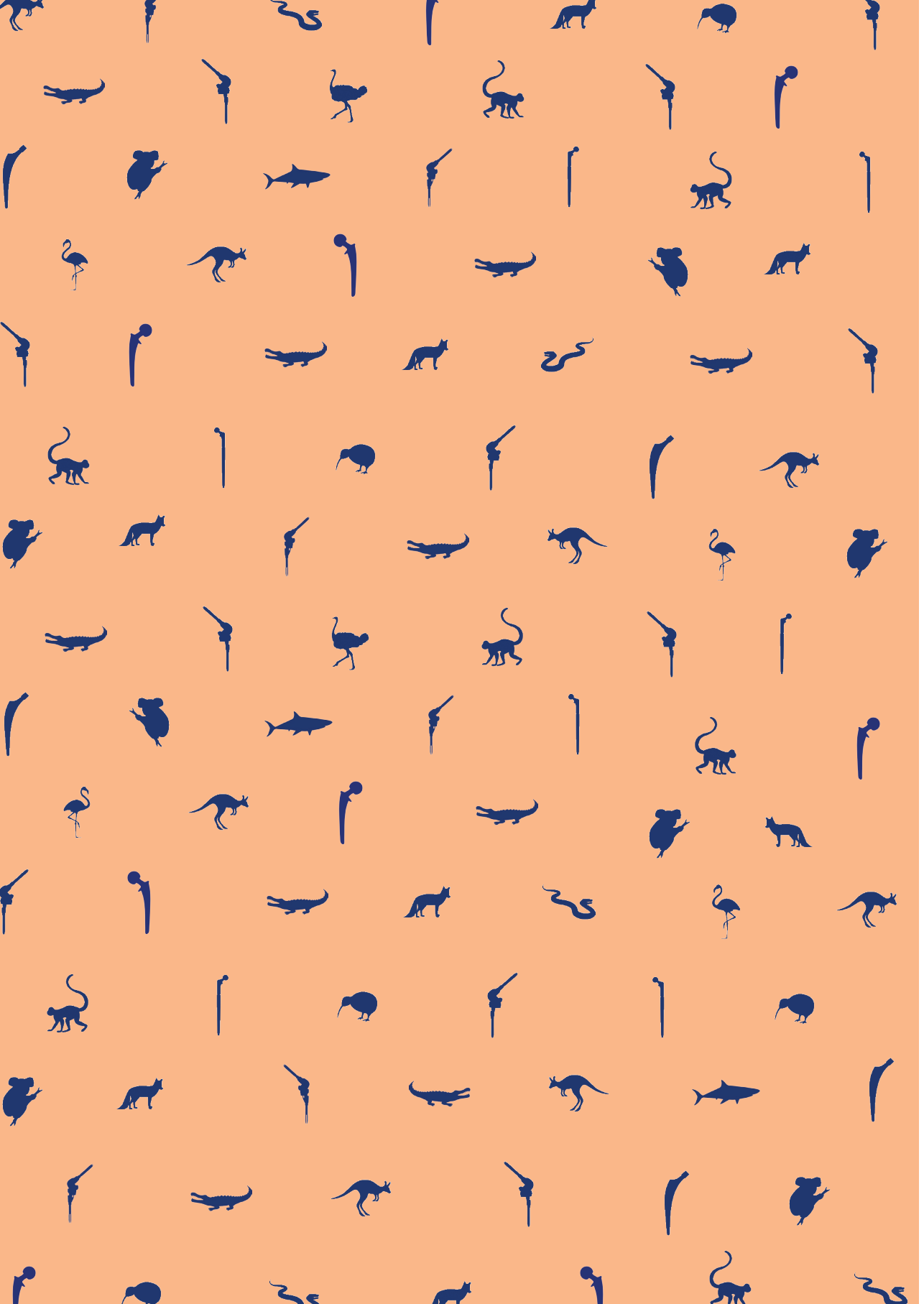

CHAPTER

11

Nederlandse samenvatting

SAMENVATTING EN DOEL VAN DIT PROEFSCHRIFT

Het aantal heup- en knieprotheses dat per jaar in Nederland en wereldwijd geplaatst wordt is al jaren stijgende. De meest ingrijpende complicatie van een prothese operatie is een prothese infectie. Het is daarom van belang meer kennis te vergaren over prothese infecties en hoe we die kunnen voorkomen behandelen.

De studies die gepresenteerd zijn in dit proefschrift hebben als doel de strategieën voor de preventie en de behandeling van prothese infecties (PJI) na primaire totale heup- of knie prothese operaties te evalueren. We hebben dit gedaan door systematische literatuur onderzoeken, retrospectieve cohort studies en een observationele cohort studie uit te voeren. Dit hoofdstuk vat de resultaten van deze studies samen en bediscussieert deze aan de hand van de doelen, zoals geformuleerd in **Hoofdstuk 1** (Introduction).

BEVINDINGEN

Deel 1: preventie van prothese infecties

Hoofdstuk 2 is een nationaal uitgevoerde enquête om in kaart te brengen welke antibiotica profylaxe protocollen worden gebruikt in Nederland, hoe de protocollen bij vroege behandeling van infectie van een heup- of knieprothese zijn opgezet en om te evalueren of deze infectie behandelingen worden geregistreerd in de Landelijke Registratie Orthopedische Implantaten (LROI). Uit deze enquête komen de volgende bevindingen naar voren:

Alle ziekenhuizen in Nederland gebruiken een antibiotica profylaxe die voldoet aan de richtlijn van de Nederlandse Orthopaedische Vereniging (NOV). Er wordt een cefalosporine antibioticum als profylaxe gebruikt, gedurende maximaal 24 uur. Negentig procent van de ziekenhuizen geeft meerdere doses cefazoline of cefuroxim gedurende 24 uur en tien procent van de ziekenhuizen geeft een eenmalige preoperatieve dosis cefazoline.

Bij een vroege prothese infectie geeft twintig procent van de ziekenhuizen aan de modulaire delen van een heup- of knieprothese niet te wisselen bij het chirurgisch schoonmaken (debridement, antibiotics and implant retention, DAIR). Dit terwijl nationale en internationale richtlijnen wel voorschrijven deze onderdelen te wisselen tijdens een DAIR procedure omdat dit een positieve invloed lijkt te hebben op de uitkomst. Ondanks dat registratie van deze procedure (wissel van een component) in de LROI verplicht is, geeft slechts 64% van de ziekenhuizen aan deze registratie

daadwerkelijk te doen. Er is dus een serieuze onderrapportage van het aantal DAIR procedures in de LROI.

Vervolgens werden data uit **hoofdstuk 2** gecombineerd met data uit de LROI betreffende revisies vanwege infectie na een primaire heup- of knieprothese binnen 1 jaar na de operatie. Het doel was om te evalueren of de voorgeschreven antibioticaprofylaxe per ziekenhuis een effect heeft op het risico op het ontwikkelen van een infectie (**Hoofdstuk 3**). Vanaf 2011 tot en met 2015 hebben 130,712 patiënten een primaire totale heupprothese en 111,467 patiënten een primaire totale knieprothese gekregen in 99 ziekenhuizen en klinieken verspreid over Nederland. Van al deze patiënten was informatie over de toegediende antibiotica profylaxe op ziekenhuisniveau beschikbaar. De resultaten van deze studie laten een vergelijkbaar risico op revisie binnen 1 jaar na de primaire operatie vanwege infectie zien voor de verschillende antibiotica profylaxe protocollen. Het hoogste risico op revisie vanwege infectie bestaat binnen de eerste 3 maanden postoperatief. Na deze eerste periode daalt het risico op revisie vanwege infectie, om rond 1 jaar postoperatief weer te stijgen. Deze laatste stijging kan een aanwijzing zijn voor het bestaan van low-grade infecties.

In **deel 1** beschreven we dat er grofweg twee verschillende typen antibiotica profylaxe protocollen in gebruik zijn bij het plaatsen van een primaire totale heup- of knieprothese in Nederland, een eenmalige profylaxe en een meermalige profylaxe tot maximaal 24 uur na operatie. We vonden, op basis van data van de LROI, geen verschil in risico op revisie vanwege infectie binnen een jaar na de primaire operatie tussen de verschillende antibiotica profylaxe protocollen.

Deel 2: resultaten van de internationale consensus bijeenkomst over orthopedische infecties

Hoofdstukken 4 en 5 beschrijven de uitkomsten van de internationale consensus meeting (ICM) over orthopedische infecties in 2018 in Philadelphia. De ICM is een internationale samenwerking van de MusculoSkeletal Infection Society uit Amerika en de European Bone and Joint Infection Society. Vierhonderd orthopaedisch chirurgen en infectiespecialisten uit 51 landen kwamen bijeen om consensus te bespreken over orthopedische infectie onderwerpen. Consensus impliceert niet dat er altijd bewijs gevonden is, maar het geeft wel een overzicht van de best beschikbare literatuur en over meningen op het gebied van infecties.

In **hoofdstuk 4** beschrijven we de consensus die is bereikt m.b.t. de behandeling van acute infecties van de heup en knieprothesen. Er bestaat een sterk uitgesproken consensus over de vier besproken onderwerpen; (1) Acute postoperatieve infecties en acute hematogene infecties dienen op dezelfde wijze behandeld te worden, met een DAIR procedure. (2) In het geval van een septische patiënt dient er, ook bij een patiënt met een acuut op chronische infectie, met spoed een chirurgische reductie van het aantal bacteriën te worden verricht door een DAIR procedure of door het verwijderen van de prothese als deze los zit, en dient de patiënt te worden behandeld met antibiotica. (3) In het geval van persisterende wondlekkage 10-18 dagen postoperatief kan een operatieve behandeling geïndiceerd zijn, bijvoorbeeld een DAIR procedure. De precieze timing van deze interventie wordt nu onderzocht in de LEAK studie. (4) Het is onbekend welke behandeling optimaal is voor een patiënt met een simultane bilaterale infectie van heup- en/of knieprothesen, maar ook dan lijkt een DAIR voor elk van de geïnfecteerde gewrichten de meest optimale behandeling te zijn.

Hoofdstuk 5 beschrijft de consensus over variabelen die een gunstige uitkomst voorspellen van een two-stage revisie van een geïnfecteerde heup- of knieprothese. Sterke consensus werd bereikt op 3 onderwerpen en zwakke consensus werd bereikt op het 2e onderwerp; (1) De optimale timing voor het uitvoeren van de second stage reïmplantatie procedure is nog onbekend, de timing wordt bepaald door de behandelend specialist op basis van zijn klinische evaluatie van de patiënt. (2) Onder strikte condities, na een uitgebreide debridement, kan een stabiel gefixeerde cementmantel behouden worden om zo schade aan het bot te voorkomen. (3) Orthopedisch chirurgen moeten voor het verwijderen van cement uit moeilijk te bereiken anatomische locaties (zoals bij protrusie in het kleine bekken) van tevoren een zorgvuldige afweging maken of de risico's van het verwijderen van dit cement opwegen tegen de voordelen hiervan. (4) Er is geen bewijs dat het gebruiken van een allograft zonder antibiotica voor het behandelen van botdefecten bij reïmplantatie van de prothese leidt tot een hogere kans op re-infectie, hoewel dit slechts met weinig bewijs onderbouwd wordt.

Deel 3: de antibiotica houdende functionele heup spacer

Hoofdstuk 6 en 7 beschrijven een tweetal studies naar de patiënt-gerapporteerde en functionele uitkomsten en de kans op een succesvolle infectiebehandeling van de antibiotica houdende functionele spacer van de heup.

Eerst hebben we een literatuurstudie gedaan om de verschillende typen spacers voor gebruik bij two-stage revisie ingrepen van de heup te vergelijken (**hoofdstuk 6**). We vergeleken de functionele uitkomst, de patiënt-gerapporteerde uitkomst, de kans op succesvolle infectiebehandeling en het voorkomen van complicaties bij patiënten die behandeld zijn met een functionele spacer, een standaard (voorgefabriceerde cement) spacer of een met de hand vervaardigde spacer. De kans op een succesvolle behandeling (respectievelijk 93%, 96% en 95% succes) en de patiënt-gerapporteerde uitkomst volgens de Harris Hip Score (respectievelijk 90, 81 en 83 punten) waren vergelijkbaar voor de verschillende types spacer. De complicaties waren evenredig verdeeld over de groepen, behalve voor het aantal spacer luxaties. De incidentie van spacer luxaties is, vergeleken met de andere groepen, hoger voor de standaard spacer (13% versus 4% en 3%). Significantie van deze uitslagen kon niet worden aangetoond vanwege heterogeniteit van de data.

Vervolgens beschrijven we in **hoofdstuk 7** de patiënt-gerapporteerde uitkomst, de kans op succesvolle infectiebehandeling en de complicaties van twee groepen patiënten die, achtereenvolgens in opvolgende tijdperiodes, behandeld zijn met een functionele spacer of een standaard cement spacer. De resultaten van deze studie laten significante verschillen zien van de patiënt-gerapporteerde uitkomstmaten (EQ-5D en HOOS) en het aantal spacer luxaties, alle ten faveure van de functionele spacer. De succeskans van de infectiebehandeling is 93% voor de functionele spacer en 78% voor de standaard spacer, door het kleine aantal patiënten is dit verschil niet significant.

Samenvattend laat **deel 3** zien dat patiënten die behandeld zijn met een functionele spacer bij two-stage revisie van de heup een vergelijkbare kans op succesvolle infectiebestrijding hebben, terwijl ze betere patiënt-gerapporteerde uitkomsten bereiken en een lager risico hebben op complicaties.

Deel 4: behandeling van prothese infecties

De succeskans van de behandeling en het complicatierisico van een prothese infectie met een coagulase-negatieve Stafylokok (CoNS) zijn beschreven in **hoofdstuk 8**. Bij twintig van de 29 patiënten met een geïnfecteerde heup en bij 11 van de 15 patiënten met een geïnfecteerde knie werd de infectie succesvol behandeld met een two-stage revisie en langdurige antibiotica behandeling. In deze kleine serie patiënten met een geïnfecteerde heupprothese was de kans op een succesvolle behandeling groter wanneer gebruik werd gemaakt van een functionele spacer (88%) vergeleken met een standaard cement spacer (71%, $p>0,05$). Bij patiënten met een geïnfecteerde

knieprothese was de kans op succesvolle behandeling groter wanneer gebruik werd gemaakt van een dynamische spacer (82%) vergeleken met een statische spacer (50%, p>0,05). Concluderend geeft de behandeling met een two-stage revisie van een geïnfecteerde heup- of knieprothese met een biofilm producerende CoNS-infectie een vergelijkbare uitkomst als met een niet-biofilm producerende bacterie in onze serie met 44 patiënten.

In **hoofdstuk 9** beschrijven we een groep patiënten die behandeld zijn met een two-stage revisie van de knie vanwege een verdenking op een geïnfecteerde knieprothese. Echter, deze patiënten voldeden niet aan de nu geldende prothese infectiecriteria. Deze patiënten (i.e. two-stage revisie, zonder prothese infectie) werden vergeleken met een matched-pair groep patiënten die vanwege een aseptische reden een one-stage revisie van de knie hebben gehad. De twee groepen werden vergeleken op functionele en patiënt-gerapporteerde uitkomsten. Postoperatief vonden we een vergelijkbare beweeglijkheid van de knie voor beide groepen. Patiënten die behandeld zijn met een one-stage revisie behalen significant betere resultaten op de subscores voor pijn en symptomen van de KOOS vragenlijst. Drie patiënten in de two-stage groep ontwikkelden een infectie tussen de twee operaties in, welke uiteindelijk succesvol behandeld werd met 12 weken antibiotica.

CONCLUSIES EN TOEKOMSTPERSPECTIEF

De studies in dit proefschrift hadden als doel de werkwijze van preventie en behandeling van prothese infecties te bestuderen. We hebben laten zien dat er geen verband lijkt te zijn tussen het aantal revisies vanwege infectie binnen 1 jaar na een primaire heup- of knieprothese en de duur van de antibioticaprofylaxe ten tijde van die primaire ingreep.

Gezien de zeldzaamheid van de prothese infectie complicatie is het essentieel dat orthopedisch chirurgen zich strikt aan de infectiecriteria en behandel richtlijnen houden bij het bepalen van het wanneer en welke behandeling voor hun patiënt.

In afwezigheid van level 1 bewijs, kunnen retrospectieve studies duiden op mogelijke associaties tussen gebruikte behandelprotocollen en de daaropvolgende uitkomsten van behandelde patiënten. Retrospectieve studies vormen hypotheses, die vervolgens prospectief getoetst moeten worden. Zowel bij prospectieve als bij retrospectieve studies hangt de kracht van de studie met name af van het aantal min of meer homogene patiënten die geïncludeerd worden. Door de lage incidentie van prothese

infecties zou het de kwaliteit van de literatuur over de behandeling prothese infecties verbeteren wanneer de data van verschillende centra worden gecombineerd. Tot op heden is het aantal multicenter retrospectieve cohortstudies over prothese infecties laag. Het kan zeer de moeite waard zijn om de krachten te bundelen, gezien de bewijskracht van het resultaat toeneemt als het aantal geïncludeerde vergelijkbare patiënten stijgt. Zeker in een klein land als Nederland zou het combineren van data uit verschillende ziekenhuizen haalbaar moeten zijn.

Ondanks alle aandacht die prothese infecties in recente jaren hebben gekregen zijn er nog vele facetten van de preventie en behandeling die nog niet onderzocht zijn. Het ontwikkelen en toetsen van behandelstrategieën zijn de basis van betrouwbare behandelprotocollen. Behandelprotocollen op basis van klinisch bewijs, dus niet alleen op basis van consensus meetings of zelfs op basis van persoonlijke ervaring, zullen leiden tot een verbeterde infectiebestrijding met oog voor zowel patiënt gerapporteerde uitkomst als voor kosteneffectiviteit.

Er zijn op dit moment enkele veelbelovende behandelopties die worden onderzocht, waarbij een goed gefixeerde prothese niet hoeft te worden verwijderd zoals dit nu het geval is. Veelbelovende resultaten zijn beschreven in ex vivo studies over onder andere inductie verhitting en nano-coatings op implantaten.[1-5]

Een patiënt-specifieke behandeling bij een specifieke prothese infectie is nog niet beschikbaar, maar het gebruik van meerdere modaliteiten, chirurgisch, antibiotisch, biologisch, technisch, in wisselende samenstelling is waarschijnlijk de toekomst in de behandeling van deze desastreuze complicatie. Waarbij na elk nieuw geleverd klinisch bewijs ook weer nieuwe vragen ontstaan en daarmee nieuwe uitdagingen voor verder onderzoek.

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APPENDICES

LIST OF PUBLICATIONS AND PRESENTATIONS

Publications:

- **Veltman ES**, Lenguerrand E, Moojen DJF, Whitehouse M, Nelissen RGHH, Blom AW, Poolman RW. *Similar risk of complete revision for infection with single-dose versus multiple-dose antibiotic prophylaxis in primary arthroplasty of the hip and knee: results of an observational cohort study in the Dutch Arthroplasty Register in 242,179 patients.* Acta Orthop. 2020 Jul 23:1-7.
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- van Dijk B, Nurmohamed RHFR, **Veltman ES**, Rentenaar B, van der Wal BCH, Vogely HC. *Outcome of DAIR procedures in different stages of infection treatment.* Poster presentation EBJIS 2019 (Antwerp).
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- **Veltman ES**, Moojen DJF, Poolman RW. *Improved Infection Eradication Rate and Patient Reported Outcome with Functional Articulating Spacers in Two-Stage Revision of the Infected Hip.* Poster presentation at EHS 2018 (the Hague).
- **Veltman ES**, Moojen DJF, Poolman RW. *Improved Infection Eradication Rate and Patient Reported Outcome with Functional Articulating Spacers in Two-Stage Revision of the Infected Hip.* Poster presentation at EBJIS 2018 (Helsinki).
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- **Veltman ES**, Moojen DJF, Poolman RW. *Improved Infection Eradication Rate and Patient Reported Outcome with Functional Articulating Spacers in Two-Stage Revision of the Infected Hip.* Presentation at Erasmus MC Infection Meeting (Rotterdam).
- **Veltman ES**, Moojen DJF, Poolman RW. *Two-Stage Revision Arthroplasty for Coagulase-Negative Staphylococcal Periprosthetic Joint Infection of the Hip.* Poster presentation at EHS 2018 (the Hague).
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CURRICULUM VITAE

Wout Veltman (1984) was born as Ewout Simon in Geldrop, as the third of eventually four brothers. Wout graduated high school at the Stedelijk Gymnasium Breda in 2003 and started his medical school at the Academic Medical Center in Amsterdam in 2005. His interests in sports and mobility soon led him to the orthopaedic department, where he performed his research fellowship (AMC) and both of his senior internships (AMC and OLVG).

After graduating, Wout kickstarted his career at the surgical department of the Amphia hospital in Breda, before transferring as a resident (ANIOS) to the st. Maartenskliniek Nijmegen and later on to the Spaarne Ziekenhuis Hoofddorp. In 2015 Wout started his orthopaedic residency which took him through exciting stages at the department of surgery of st. Antonius hospital, and the orthopaedic departments of OLVG, st. Antonius hospital and University Medical Centre Utrecht and briefly at the trauma department of UMCU. Wout participated in the travelling fellowships of the NVOT (trauma) and has been elected to join the travelling fellowship of the EBJIS (orthopaedic infections). At the end of 2020 Wout will finish his orthopaedic specialty training at the orthopaedic department of OLVG Amsterdam.

Next to his residency Wout was a member of the VOCA board, and was involved in the organisation committees of the second edition of Sporthopedie in 2018 and the FORTE summit in 2020.

During his study and residency years Wout was an industrious midfielder for the renowned football team Swift 4, and he is a former winner of the illustrious Swift 4 Player of the Year Award. In 2017 Wout married Deli, his girlfriend of more than 10 years. With the birth of their daughter Vosse, they started their family in 2019.

Following the defense of this thesis and his registration as an orthopaedic and trauma surgeon Wout will travel to Sydney in Australia where he has secured a position as fellow to professor William Walter. He is looking to gain experience in trauma and revision hip and knee arthroplasty and to pick up a tan and broaden his horizon.