Strategies in prevention and treatment of prosthetic joint infections

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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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