Chapter 10

General discussion and future perspectives
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The studies in this thesis aimed to examine and evaluate the risk factors and treatment strategies for early prosthetic joint infection (PJI). PJI is one of the most serious complications after joint arthroplasty and can develop at any time point after surgery.\textsuperscript{1,2} Although it is important to prevent all types of PJI (early PJI, late PJI and hematogenous PJI), the studies in this thesis focused solely on patients with early PJI, as a large proportion of PJI occurs in the early post-surgical course. The first part of this thesis evaluated patient groups at risk for PJI, including obese patients, oncology patients and patients with prolonged wound leakage after total hip arthroplasty (THA) and total knee arthroplasty (TKA), while the second part of the thesis examined factors that can influence the treatment success of DAIR, including patient selection, use of local antibiotics during DAIR and the timing of DAIR. The present chapter presents a general discussion on the main findings of the studies in this thesis and offers future perspectives and implications for clinical practice.

Part 1: Evaluation of patients at risk for early PJI

Even though we cannot see them, microorganisms are everywhere. They are present in the air, in water, on the surface of the skin and in about each object in an operating room. Even though many preventive measures are put in place to prevent microorganisms from infiltrating the joint during total joint arthroplasty surgery, complete protection is an impossibility. Fortunately, the immune system provides additional protection by eradicating microorganisms that infiltrate the joint. Prevention of PJI is therefore aimed at identifying and eliminating two types of risk factors: 1) factors that increase the risk of exposure of the joint to microorganisms, and 2) factors that limit the host’s ability to eradicate contamination of the joint with microorganisms. Literature identified that an important type-1 risk factor is prolonged wound leakage with or without development of a sinus,\textsuperscript{3,4} as a leaking wound increases the risk of exposing the joint to microorganisms by providing a \textit{porte d’entrée}. Hence patients at risk for prolonged wound leakage should be carefully evaluated postoperatively, to identify and treat postoperative complications at an early time point and thereby minimize the risk of PJI. Type-2 risk factors identified in previous studies include obesity, diabetes mellitus, oncological conditions and rheumatoid arthritis.\textsuperscript{5,6} Knowledge about these risk factors can be used to estimate the risk of PJI before implantation of the joint arthroplasty. This risk estimation can support the decision-making process of both patient and health
care professional on: 1) whether or not to perform joint arthroplasty surgery, and 2) whether or not to deploy additional strategies before, during and after joint arthroplasty surgery to prevent PJI. Moreover, efforts towards optimizing these risk factors can minimize the risk of PJI, for example by performing the joint surgery when the immune system is the least compromised, by reducing weight or by improving antibiotic prophylaxis regimens. The studies in this thesis focused on three patient categories at increased risk for PJI: obese patients, oncology patients and patients with prolonged wound leakage.

**Obese patients**

Obesity is a major health concern worldwide, with a tripled number of obese patients in recent decades. Although many papers have shown that obesity is a risk factor for PJI, the causes for this increased risk remain unclear. There are several factors that contribute to impaired wound healing and thus prolonged wound leakage in obese patients: 1) Obese patients have abundant subcutaneous tissue, which is relatively avascular. 2) Obese patients are at increased risk of formation of pooled blood or serous fluids due to large dead space. The formation of these hematomas or seromas increase the internal pressure on the wound and sutures, which further impairs wound healing. 3) In order to achieve proper cellular response in the wound healing process the body needs sufficient proteins, vitamins and minerals. Since obese patients suffer from a paradoxical malnutrition, resulting from a calorie-dense diet high in carbohydrates and fats and low in vitamins and minerals, they have nutritional deficiencies that impede such cellular response.

In addition, the results of chapter 4 showed that periprosthetic hip infections in obese patients are caused by different microorganisms than in non-obese patients. Obese patients had higher rates of polymicrobial infections and more infections with *Enterococcus* species. Moreover, severely obese patients with hip PJI had more infections with Gram-negative rods, mainly *Proteus* species and *Morganella morganii*. These results support the hypothesis of abundant colonization with multiple microorganisms in the groin, which may be due to the large surface of skin with favorable moist conditions for microorganisms in the skin folds of obese patients. This implies that preventive measures should be adapted for obese patients receiving THA.

In future research the orthopaedic infection community should explore feasible adaptations of these preventive measures. There are several options to
this end. First of all, obese patients could receive a higher dosage of cefazolin, considering the higher minimum inhibitory concentration (MIC) of cefazolin for Proteus species and the fact that currently applied cefazolin dosage may not be sufficient to achieve adequate tissue concentrations in obese patients.\textsuperscript{12-15} The newest SWAB guideline (Stichting Werkgroep Antibiotica Beleid) already advises administering 3000mg cefazolin to patients with a BMI >40kg/m\textsuperscript{2} (instead of the previous 2000mg).\textsuperscript{16-17} Our results nonetheless indicate that the higher dosage of cefazolin may also be beneficial for patients with a BMI >35kg/m\textsuperscript{2} receiving THA, since the rate of Proteus species was significantly higher in severely obese patients. It will be interesting to compare incidences of PJI before and after implementation of this new guideline, especially with regard to the number of infections caused by Proteus species.

Secondly, the type of antibiotic prophylaxis in obese patients during primary hip arthroplasty could be modified to cover a broader spectrum of microorganisms - for example, by adding a glycopeptide such as vancomycin or teicoplanin to the standard antibiotic prophylaxis regimen, as these types of antibiotics cover Enterococcus species. Gram-negative microorganisms, commonly found in obese patients with hip PJI, are inherently resistant to both vancomycin and teicoplanin. Substituting cefazolin with cefuroxime would be more effective in providing full coverage for Gram-negative microorganisms, but unfortunately cefuroxime does not cover Enterococcus species. Combining a glycopeptide with cefazolin would be the preferred option, especially when the cefazolin dosage is adjusted to the BMI. Although this raises the concern of developing antibiotic resistance, it may be a minor concern since antibiotic prophylaxis is only administered for a limited, maximum period of 24 hours. While some studies already compared the efficacy of various antibiotic prophylaxis regimens in reducing infection rates after joint arthroplasty,\textsuperscript{18-20} only one considered BMI in their results. Tornero et al. showed a reduction of PJI rates in obese patients receiving cefuroxime plus teicoplanin compared with cefuroxime only.\textsuperscript{21} This reduction was mainly observed for PJI due to Staphylococcus aureus, which supports the hypothesis that the dosage of antimicrobial prophylaxis may be insufficient for obese patients, as Staphylococcus aureus should be fully covered by cefuroxime.

Thirdly, disinfection of the hip region could be performed more thoroughly in patients who will receive THA. Chlorhexidine-alcohol 2% should be applied as disinfectant, as it is proven to be more effective than povidone-iodine in
reducing postoperative infections.\textsuperscript{22} Currently there are no studies comparing the efficacy of chlorhexidine-alcohol with povidone tincture in 75\% alcohol though. Moreover, obese patients could be treated with mupirocin nasal cream preoperatively and be required to take chlorhexidine gluconate showers for five days before index surgery in order to decolonize the skin.\textsuperscript{23} Although this is only proven to effectively reduce infections caused by \textit{Staphylococcus aureus} (which is not the main cause of the higher number of PJI's in obese patients), a substantial number of infections could be prevented by standard application of this regimen in obese patients.

Lastly, since surgical wounds in obese patients are prone to prolonged wound leakage, it is essential that obese patients be evaluated more extensively after joint arthroplasty, especially after THA. Although follow-up after joint arthroplasty differs per hospital, as shown by the survey on wound leakage among Dutch orthopaedic surgeons, obese patients (especially with BMI >35\textsuperscript{2}kg/m\textsuperscript{2}) should be re-evaluated at the outpatient clinic one week after index surgery. In this way wound complications can be detected at an early time point and treated adequately.

\textbf{Oncology patients}

Patients with bone tumors requiring joint arthroplasty after resection of tumor tissue are at increased risk for developing PJI. The prevalence of oncologic PJI is 7\% to 28\%\textsuperscript{24-26} compared with approximately 1\% for regular PJI.\textsuperscript{27} Multiple factors cause this increased risk, such as immunodeficiency due to radiotherapy or chemotherapy, longer duration of surgery, larger wounds and use of larger implants due to extensive tumor resection.\textsuperscript{28} Unfortunately, little is known specifically about oncologic PJI, which is shown in the literature review presented in this thesis. Most guidelines for oncologic PJI are therefore derived from research on patients with regular PJI. Although this may work for some aspects of PJI, such as diagnostic criteria, several topics need research specifically conducted on patients with oncologic PJI.

First of all, administration of adequate antibiotic prophylaxis is important to reduce the risk of PJI in oncology patients. In regular total joint arthroplasty, there is consensus that antibiotic prophylaxis should not be administered for longer than 24 hours after index arthroplasty.\textsuperscript{29} There is no consensus on antibiotic prophylaxis in oncology patients though. Since oncology patients represent a heterogenous population, it is difficult to compare studies on
this topic. A systematic review by Racano et al. suggests that administering antibiotic prophylaxis longer than 24 hours is beneficial for oncology patients. A multicenter randomized controlled trial called the PARITY trial (Prophylactic Antibiotic Regimens In Tumor surgery) is currently being conducted to compare the efficacy of 24 hours with 5 days of antibiotic prophylaxis. These results may lead to the composition of an evidence-based guideline for antibiotic prophylaxis in oncology patients.

Secondly, the application of coated arthroplasties can have positive effects on the reduction of oncologic PJI. One of the most reported types of coated arthroplasties is silver-coated arthroplasty. Because of its effective local antimicrobial activity and relatively low toxicity, the silver coating seems a viable option for oncology patients. Only few patients reported local side effects of the silver, such as dermal argyria. Other coating options include the use of iodine-coated arthroplasty, which showed potential in a study by Tsuchiya et al. This type of coating should be examined more thoroughly before it is standardly applied in clinical practice.

Thirdly, the timing of chemotherapy and radiotherapy can influence the risk of PJI. Although radiotherapy is not routinely applied in the treatment of bone tumors, it may be used preoperatively for radiosensitive tumors (such as Ewing’s sarcoma) or postoperatively in case of inadequate surgical margins, poor response to chemotherapy or local recurrence. Infection rates are 23% in patients who received radiotherapy before index arthroplasty and 35% when radiotherapy was started after index arthroplasty. This is because radiotherapy impairs wound healing by damaging fibroblasts, which leads to necrosis, slow growth of skin cells and thereby reduced strength of the wound. Neo-adjuvant chemotherapy is often applied in bone tumors. A review on the effects of neo-adjuvant chemotherapy showed that immunodeficiency after chemotherapy is associated with an increased risk of PJI, although others did not find any effect of chemotherapy on infection rate. While radiotherapy and chemotherapy likely influence the risk of PJI in oncology patients, there is no established optimal timing for oncologic tumor resection. This should be examined in future studies.

**Patients with prolonged wound leakage**

Prolonged wound leakage is a difficult problem since wound leakage can be a symptom of an already existing PJI or a risk factor for developing PJI (by...
providing a *porte d'entrée* for microorganisms⁴). Surgical wounds may also show prolonged leakage for reasons other than infection (such as hematoma, seroma or fatty necrosis) and take longer to heal without developing an infection, especially in certain patient categories such as obese patients or patients on anticoagulant medication. If prolonged wound leakage is caused by an infection, surgical treatment is preferred and typically consists of DAIR.⁴¹⁻⁴³ If prolonged wound leakage is caused by factors other than infection, non-surgical treatment is preferred, aiming to prevent the development of a PJI. Non-surgical treatment consists of relative rest (bed rest and no exercise), pressure bandages and wound care with sterile bandages.⁴²,⁴⁴ Unfortunately, distinguishing between these types of wound leakage is often challenging, which hinders adequate treatment and optimal timing of treatment of prolonged wound leakage.

Remarkably, literature on this topic is scarce; this is clearly shown by the literature review in this thesis. Because of this lack of scientific evidence, there are no national or international evidence-based guidelines. Most current guidelines are based on consensus, in particular the international consensus meetings on prosthetic joint infections in 2013 and recently in July 2018 in Philadelphia.²⁹,⁴²,⁴⁵ Moreover, many orthopaedic surgeons base their decision on the treatment of prolonged wound leakage solely on their own past experiences. This is clearly demonstrated in the results of the survey among Dutch orthopaedic surgeons on current clinical practice for prolonged wound leakage, indicating wide variation in all aspects of its diagnosis and treatment.

Interestingly, only half of the hospitals had a protocol for prolonged wound leakage and only 26% used this protocol regularly. This reveals the difficulty of composing a protocol due to the lack of scientific evidence. It also indicates that prolonged wound leakage is a complex problem for which orthopaedic surgeons feel it is necessary to evaluate each patient individually to decide on the best treatment. Although an individual approach can be beneficial for patients, it also has disadvantages. If a patient has prolonged wound leakage, the timing of surgical treatment is usually considered for several days; in other words, it may take several days before the medical practitioner decides whether it is necessary to perform a DAIR. This results in uncertainty and concern for the patient, who may be fearful of a second surgical procedure and worry about potentially more extensive surgeries such as revisions. Standardized use of a protocol in hospitals reduces uncertainties for patients, since they know that
surgical treatment will be performed when wound leakage persists beyond a certain time point.

Composing a protocol for prolonged wound leakage not only benefits patients, it also provides advantages for medical practitioners. The current lack of evidence-based guidelines and the large variety in current clinical practice stresses the need for high-quality evidence on this topic. The results of the LEAK study can provide such high-quality evidence, which will help medical practitioners in the clinical decision-making process. Besides the main aim of the LEAK study to evaluate the timing of DAIR in patients with prolonged wound leakage, there are several other topics of interest. By collecting data on C-reactive protein (CRP) values at several time points after index arthroplasty, the LEAK study can assess the possibility of estimating risk of infection in patients with prolonged wound leakage based on the postoperative trend of the CRP values. Moreover, data on the clinical aspect of the surgical wound at various time points after index arthroplasty are collected, which may indicate that, for example, patients with hematoma experience prolonged wound leakage more often without developing an infection. Patient-related factors such as BMI, comorbidities and medication are also collected, with the ultimate goal to estimate risk of infection for various clinical profiles according to number of days and classification of wound leakage. To illustrate: a patient with obesity and steroid therapy with wound leakage class 2 at day 9 has a 43% estimated risk of infection. Drafting such a prediction model will greatly support the clinical decision-making process.

As there is still no optimal tool to diagnose PJI without performing surgery, and certainly not for patients with prolonged wound leakage, it would be interesting to test the accuracy of various synovial biomarkers for diagnosing PJI in these patients. Two promising biomarkers are alpha-defensin and leukocyte esterase, with sensitivity and specificity reaching nearly 100% for alpha-defensin, and 81% sensitivity and 97% specificity for leukocyte esterase. Advantage of leukocyte esterase is that it is a point-of-care test that can be used as a bedside marker, while alpha defensin is tested by immunoassay, whose results take longer to obtain. Moreover, the alpha-defensin test is very expensive. A cheaper biomarker would be calprotectin, which showed high accuracy in a recent study by Wouthuyzen-Bakker et al. It is already used routinely as a fecal marker in patients with inflammatory bowel disease and is currently available as a point-of-care test. However, neither biomarker has
yet been tested to diagnose PJI in patients with prolonged wound leakage. Another option would be to culture synovial fluid. Its main benefit is that the causative microorganisms can be identified before DAIR, so that adequate antibiotic treatment can be started immediately after obtaining intraoperative cultures. A downside is that there is little time to wait for positive cultures in patients with prolonged wound leakage. Medical practitioners will only wait a few days before proceeding to DAIR, at which point it will only culture virulent microorganisms. Hence synovial fluid culture cannot be used to rule out PJI in patients with wound leakage, as it would be necessary to wait two weeks before culture results are definitively negative. Synovial fluid culture can however still be used to rule in PJI, as the specificity of 95% is indicative of a few false-positive cultures. It would be an option to test samples of wound exudate, since these are available at any time in patients with wound leakage and can be obtained non-invasively. Cultures of superficial exudate samples have proven to be inadequate though. This is why new biomarkers should be developed and examined for this new method of diagnosing PJI in patients with prolonged wound leakage. Currently, bacterial toxins seem a viable option, although the accuracy of these toxins should be studied more extensively.

Part 2: Improving treatment strategies for early PJI

Although the main objective should be to prevent PJI, once PJI develops it should be effectively treated. The ideal treatment consists of selecting the right treatment modality for the specific patient and optimally administering it. There are several options to treat early PJI. While two-stage revision arthroplasty provides the highest cure rates (ranging from 85% to 100%), it is accompanied with high morbidity and mortality as well as high health care costs. DAIR can treat PJI without the need for removal of the prosthesis, but has an evidently lower cure rate than two-stage revision (ranging from 40% to 90%). Although it is useful to try to cure PJI with less invasive surgery (DAIR) before proceeding to revision surgery, there are some downsides. First of all, it is not yet clear whether performing a DAIR prior to revision surgery decreases the cure rate of revision surgery. Moreover, if the infection is not cured by DAIR patients are subjected to additional surgical procedures before the implant is removed and infection is treated. Still, there are many benefits of DAIR over revision surgery, such as faster postoperative rehabilitation, preservation of bone stock, decreased risk of intraoperative fractures and shorter duration of
the surgical procedure. These benefits outweigh the downsides of DAIR, but do stress the importance of proper patient selection and excellent performance in order to optimize DAIR cure rates.

**Selecting patients for DAIR**

To explain the large variation in success rates of DAIR, previous studies identified several patient-related, surgical and microbiological risk factors for DAIR failure. For patient-related risk factors, they found that a high ASA score, arthroplasty indicated for fracture, longer duration of symptoms, and high serological inflammatory markers are related to an increased risk of DAIR failure. Moreover, surgical risk factors such as arthroscopic debridements, purulent discharge at the site of the implant, and DAIRs without exchange of modular components also increase the risk of DAIR failure, just as culturing *Staphylococcus aureus* as causative microorganism.

Although all these factors are known to contribute to an increased risk of DAIR failure, so far there is no practical tool available that can estimate this risk for each specific patient, which could help orthopaedic surgeons in their decision-making process. A tool for predicting DAIR failure should meet two conditions: it should be available preoperatively and be easy to use, to facilitate its implementation in daily clinical practice. Tornero et al. designed a predictive tool that meets both conditions: the KLIC score, which consists of five preoperative patient-related risk factors: 1) chronic renal failure (Kidney), 2) Liver cirrhosis, 3) Index surgery, 4) Cemented prosthesis and 5) CRP >115 mg/L (KLIC). Our results showed that the KLIC score can significantly predict DAIR failure, where a higher KLIC score corresponds with a higher failure rate. Despite the significant predictive value of this risk score, our study showed a much lower accuracy than Tornero et al.; this could be ascribed to differences in local epidemiology, patient characteristics and surgical techniques. For example, orthopaedic surgeons in our cohort performed exchange of modular components in only 21% of patients, while Tornero et al. did in 72.9%. Remarkably, the exchange of modular components was not associated with DAIR failure in this study, while previous literature clearly identifies it as a risk factor. It is nonetheless advisable to exchange all modular components during a DAIR procedure for three reasons: firstly, it is important to create free space for optimal debridement (without removal of modular components the deeper compartments of the joint cannot be irrigated and debrided.
thoroughly); secondly, any microorganisms and biofilm present on the modular components should be removed and clean components reinserted; finally, removed modular components can be used to diagnose PJI when sent for sonication.

The lower accuracy in our cohort indicates that medical practitioners should be cautious when implementing this risk score routinely in daily clinical practice. Nevertheless, our study did show that the score is useful in patients with low (<3.5 points) or high (>6 points) KLIC scores. In patients with low KLIC scores medical practitioners should always perform a DAIR procedure before turning to other, more invasive surgical treatment modalities. However, in patients with high KLIC scores and therefore a high estimated risk of DAIR failure of 60% to 90% an orthopaedic surgeon may consider a different treatment approach with a higher chance of infection control. The downside of choosing a different treatment approach in patients with a high KLIC score is withholding a less invasive surgical treatment from patients while there is a chance that they may benefit from this milder treatment. Moreover, medical practitioners should consider the great impact of revision surgery on patients’ quality of life when choosing to perform extensive revision surgery without trying to cure the infection with DAIR. Due to the relatively low accuracy of the KLIC score in our cohort, medical practitioners should not base this decision solely on the KLIC score but should consider the treatment options per individual patient. Currently the preferred strategy is that all patients can undergo the DAIR procedure to try and cure the infection, but in patients with high KLIC scores other treatment options or postoperative suppressive antibiotic treatment should be considered to optimize the chances of infection control.

Future research should aim to develop a preoperative risk score for DAIR failure with a higher accuracy than the KLIC score. In our cohort we found it important for the CRP value and arthroplasty indicated for fracture to be included in the risk score. Other variables such as age, exchange of modular components and number of days from arthroplasty to DAIR could also be included. The CRIME80 score is currently used to predict DAIR failure in patients with hematogenous PJI. It consists of seven variables, each with appointed scores, where a higher CRIME80 score is associated with a higher risk of DAIR failure: COPD (2 points), CRP >150mg/l (1 point), rheumatoid arthritis (3 points), arthroplasty indicated for fracture (3 points), male (1 point), exchange of modular components (-1 point), age >80 years (2 points). Although it is
preferable to use the same risk score for DAIR failure in both early PJI and late acute PJI, the score remains to be validated for patients with early PJI.

**Use of gentamicin beads and sponges**

Improving outcome after DAIR by administering local antibiotics is a longstanding strategy in Dutch hospitals, yet the beneficial effect of these antibiotics has never been demonstrated and its use remained confined to the Netherlands. In theory, achieving high concentrations of antibiotics at the site of infection and providing dead space management should help cure PJI. Because of the local effect of the gentamicin-impregnated beads and sponges in the joint cavity, systemic toxic side effects are uncommon, although Swieringa et al. have reported a decrease in renal function after application of gentamicin-impregnated sponges.

The application of gentamicin-impregnated beads and sponges does not seem to influence clinical outcome though. One study by Kuiper et al. demonstrated that applying gentamicin-impregnated sponges is associated with a lower failure rate of DAIR while using gentamicin beads showed higher failure rates, although these differences were not observed in the multivariate analysis. Two different studies did not show any beneficial effect of gentamicin beads, while other studies only described the outcome of routinely using gentamicin beads, without comparing with controls. Chapter 6 of this thesis showed higher failure rates after DAIR in the gentamicin group, even after propensity score matching for confounding factors. Moreover, patients on whom gentamicin-impregnated beads or sponges were used needed implant removal twice as often than control patients (5.2% vs 2.6%). Although these results were not statistically significant, they clearly demonstrate that applying gentamicin-impregnated beads or sponges does not improve the outcome after DAIR and may even have adverse effects. Accordingly, its use for this indication should be discontinued.

A reason for the lack of efficacy of local gentamicin may be its reduced activity in the joint cavity in patients with PJI, due to a low pH and low oxygen level caused by the presence of a biofilm. Moreover, local gentamicin levels may be below the MIC levels, reducing their efficacy. Even though both gentamicin beads and sponges can get gentamicin levels far above the MIC levels in the joint cavity, the release of gentamicin is maximal in the first few days after insertion and decreases afterwards. For instance: gentamicin sponges
release up to 95% of their antibiotics in the first two hours after insertion.\textsuperscript{97} After releasing gentamicin, the beads and sponges lose their purpose and can be perceived as a foreign body. Indeed, Neut et al. demonstrated bacterial growth on the majority of removed gentamicin-impregnated beads, which suggests that these beads may preserve the infection rather than cure it.\textsuperscript{90}

Future studies should assess whether applying local antibiotics can be useful when using other types of antibiotics and antibiotic carriers. Vancomycin could be an alternative to gentamicin, as the efficacy of vancomycin does not decrease when used in an environment with low pH and low oxygen levels, which is usually the case in PJI. Vancomycin can be administered as a powder, so it does not necessitate a second DAIR procedure to remove an antibiotic carrier and does not become a foreign body. Recent studies showed good results with use of vancomycin powder during DAIR procedures.\textsuperscript{98,99} A large systematic review on vancomycin powder in 6701 cases of spinal surgery showed nephrotoxicity in one case and ototoxicity in one case.\textsuperscript{101} A different study showed a higher rate of wound complications when vancomycin powder was administered during total hip arthroplasty.\textsuperscript{102} Future studies are warranted before vancomycin powder is applied standardly, but its application is encouraged for patients at a high risk of DAIR failure, estimated by calculating the KLIC score or CRIME80 score.\textsuperscript{83}

\textbf{Optimal timing of DAIR}

Although there are no absolute contraindications to perform a DAIR procedure in patients with early PJI, DAIR is only advised when the risk of failure is acceptable. The risk of failure depends on multiple host- and implant-related factors, as described above. Most of the guidelines applied to decide whether it is viable to perform a DAIR procedure are based on duration of symptoms and time interval from index arthroplasty to DAIR. Most authors suggest that DAIR should be performed within a few days of the onset of symptoms in order to achieve infection control.\textsuperscript{64,67,73} Moreover, current guidelines suggest that DAIR should not be performed when PJI develops more than 30 days after index arthroplasty.\textsuperscript{100}

Using a guideline solely based on number of days from index arthroplasty to DAIR has advantages. Whereas the duration of symptoms is usually subjective, the number of days from index arthroplasty is objective. Besides, the precise onset of symptoms can be difficult to establish, as it is confounded
by the physiological healing process, for example in case of pain or wound leakage in the early post-surgical course. The study in this thesis showed that the time interval from index arthroplasty to DAIR is not a reliable predictor for treatment success of DAIR in early PJI. Although treatment failure was highest when performing DAIR in the late post-surgical course (7-12 weeks), DAIR was successful in approximately 60% of these patients. This still makes it a viable treatment option when performed more than 30 days after index arthroplasty, in contrast to previously published guidelines.100

The increase in failure rates when DAIR was performed more than six weeks after index arthroplasty is supported by previous studies evaluating the time to develop a mature biofilm. These studies showed that a biofilm is already evident within two weeks of inoculation with microorganisms.103-105 In the complex process of biofilm formation, embedded microorganisms become unresponsive to almost any antibiotic treatment because of multiple phenotypic and genotypic changes.106,107 Within six weeks a mature biofilm has developed, at which time point PJI can no longer be cured with antibiotics only, without removal of the implant. The results in this thesis illustrate that the development of a biofilm is a variable process that depends not only on time but also on the causative microorganism, the size of inoculum that contaminated the wound during surgery, and the host.108,109

Future studies should aim to compose a predictive model for the time needed to form a mature biofilm. Since this depends on multiple variables, in vitro studies are probably needed first, adding variables one at a time. For example, time until formation of a mature biofilm should be evaluated for different microorganisms. Next, time until formation of a mature biofilm should be examined for different inoculum sizes in each individual type of microorganism. This should be followed by in vivo studies, where time until formation of a mature biofilm should be examined per site of infection, as this may vary per type of joint. Complementarily, differences in host-related factors should be tested, such as various concentrations of white blood cells at the site of infection. Unfortunately, even if such a prediction model could be composed, not all these variables can be determined in patients with PJI, like the inoculum size that contaminated the wound during surgery. Another useful option when evaluating time from index arthroplasty to formation of a mature biofilm is the use of fluorescent biomarkers which can visualize the progress of biofilm formation in the joint. Current studies have used genetically encoded
fluorescent proteins to identify the stage of biofilm formation. So far these techniques have only been studies in vitro, so there is no solution yet that can be applied in the clinical situation of PJI. Future studies should aim to investigate the applicability of the real-time administration of fluorescent proteins, so that the presence and stage of a biofilm can be observed intraoperatively using a fluorescence scope. Until more is known about time to formation of a mature biofilm, DAIR should be considered a viable treatment option in patients with PJI presenting within 90 days of index arthroplasty.

**Barriers and facilitators in the LEAK study**

Unfortunately, the results of the LEAK study cannot be presented in this thesis, as inclusion is behind schedule. Although a large group of 38 Dutch hospitals are participating in this multicenter randomized controlled trial, it was not yet possible to include the necessary number of 388 patients. There are several reasons for this. Firstly, due to lengthy procedures for assessing local feasibility in the participating hospitals (which take on average 150 days), a large number of hospitals started at a later time point than the initially estimated date of 1 February 2017. For future multicenter clinical trials, national authorities should ensure prevention of unnecessary additional procedures, especially since conducting a second medical ethical examination is against national regulations. For that reason, ethical approval of the coordinating center should be considered sufficient to approve local feasibility, which is not yet the case at the moment. This issue unnecessarily hampers clinical studies and should be given high priority on the national research agenda.

Secondly, it appears that orthopaedic surgeons are hesitant to randomize patients, as they are used to their own treatment methods and believe that either surgical or non-surgical treatment is better for a particular patient, even though there is no evidence to support that statement. This viewpoint is especially interesting, since the orthopaedic community itself has stated that the topic of prolonged wound leakage constitutes an important knowledge gap. Surgeons are hesitant to perform a DAIR procedure in patients with a low risk of PJI, given the uncertainty as to whether the joint is infected. If there is no current infection, the DAIR would be performed too soon and unnecessarily, and this second intervention would be adding a risk of introducing infection. Still, ongoing wound leakage is a risk factor for developing an infection by providing a porte d'entrée for microorganisms, so postponing DAIR may also
lead to an increased risk of PJI. Unfortunately, the optimal timing of DAIR remains to be established, although the LEAK study can improve insights on this important topic. A solution offered for the hesitance toward randomization is assessment of the patient by an independent surgeon (i.e. a colleague). Moreover, in each regional training group of orthopaedics (ROGO) an ambassador is available for consultation about patient eligibility. And yet the optimal solution is actually quite simple: each patient with prolonged wound leakage should be randomized, so that the type of treatment is automatically chosen by randomization.

Thirdly, identification of eligible patients for randomization is difficult in hospitals where patients are discharged one to three days after index surgery. These patients are usually checked at the outpatient clinic at 14 days, 6 weeks or 3 months, which is too late for randomization. Even though the participating hospitals give these patients clear instructions to contact the hospital if wound leakage persists for longer than 5 to 7 days, most patients fail to do so, or do it too late (e.g. after 14 days). An innovative app will be introduced soon that can improve identification of these patients: the Wound care app is an application on mobile phone or tablet in which patients state the amount of wound leakage and signs of infection daily for the first 30 days after total joint arthroplasty. Based on an algorithm, patients receive a pop-up message to contact the hospital in case of an increased risk of infection or wound leakage lasting longer than 5 to 7 days. This will hopefully help identify patients earlier. In a pilot study recently conducted at Leiden University Medical Center and Alrijne Hospital by H. Schepers, the Wound care app showed good feasibility and patients reported that the app was easy to use. The Wound care app is currently being used in several hospitals participating in the LEAK study.

Finally, orthopaedic surgeons are worried about receiving negative reviews on inspection by insurance companies, because of having performed more DAIR procedures in the context of the LEAK study. All orthopaedic arthroplasties are registered in the Dutch Arthroplasty Register (LROI). When revision surgery is needed, this is also registered in the LROI, including the reason for revision (such as infection or aseptic loosening). When exchange of modular components is performed during a DAIR procedure, this is registered as revision surgery due to infection. Hence performing a high number of DAIRs with exchange of modular components can be incorrectly interpreted by insurance companies as performing a high number of revisions because of
infection. The Netherlands Orthopaedic Association (NOV) sent a letter to the major insurance companies to clarify these concerns, so participating hospitals do not need to worry about this issue anymore. It may nonetheless be a good thing to modify the registration in the LROI so that DAIRs can be registered as such, especially since performing a higher number of DAIRs could be perceived as beneficial as they can prevent the need for more extensive revision surgery in case of infection.

**Future perspectives**

Unfortunately, there are only a limited number of topics that can be explored in the scope of a thesis. Many other interesting topics remain unsolved and should be examined in the future. Additional questions and hypotheses arose while investigating the topics described in this thesis. Some of the most interesting subjects to investigate in the future are described below.

*Is it useful to perform a second DAIR if infectious signs persist after the first DAIR?*

The topic of performing multiple DAIRs has not been studied extensively, as most studies regard the need for further surgical procedures as DAIR failure. Studies that did assess this topic displayed different results. While Moojen et al. report similar results for single and multiple DAIRs,111,112 and Mont et al. describe good results for second and third DAIRs,113 others describe higher failure rates for second DAIR.76,81 Analyses of our cohort of 386 patients showed comparable failure rates for the first and second DAIR (unpublished data). Failure rates of a third DAIR were also assessed, but this group was too small to draw reliable conclusions. It would be interesting to compare the results of a protocol in which patients with failed DAIRs are treated with revision surgery to a protocol in which patients with failed DAIRs are treated with a second and, if necessary, a third DAIR.

*Is it useful to irrigate the joint with povidone-iodine or chlorhexidine-alcohol during DAIR?*

Currently, most medical practitioners irrigate the joint with saline pulse lavage during DAIR. It is postulated that povidone-iodine and chlorhexidine-alcohol
are more effective in treating the infection. Both agents are frequently used to prevent PJI\textsuperscript{22,114} but not yet very often in its treatment. A recent study showed good results of using povidone-iodine lavage during DAIR.\textsuperscript{115} Also, chlorhexidine-alcohol lavage showed promising results in an \textit{in vitro} study,\textsuperscript{116} but future studies are warranted before these solutions can be implemented in daily clinical practice - especially since local effects on soft tissue and systemic effects from intra-articular appliance are unknown. It would be interesting to compare the efficacy of povidone-iodine, chlorhexidine-alcohol and saline in a randomized controlled trial.

**How many dosages of prophylactic antibiotics should be administered to adequately prevent PJI?**

In the prevention of PJI it may be equally effective to give one dosage of antibiotic prophylaxis instead of three dosages. A systematic review including four randomized controlled trials could not find any evidence that three dosages are more effective than one.\textsuperscript{117} Unfortunately, the quality of evidence of these trials was very low according to the GRADE criteria. Additional trials are therefore warranted.

**Which method of wound closure best prevents wound leakage and PJI?**

For deep closure, a biomechanical study showed that microorganisms adhere less to barbed sutures than to conventional braided sutures (such as Vicryl).\textsuperscript{118} Moreover, barbed sutures allow for faster closure.\textsuperscript{119} For superficial closure, several studies found no differences in number of patients with wound leakage and superficial wound infections between staples, sutures and adhesives.\textsuperscript{120-122} A recent study by Roerdink et al. shows that adding a subcuticular layer of continuous sutures reduces the incidence of prolonged wound leakage from 11.7% to 1.9%. The incidence of PJI decreased from 1.5% to 0.4%.\textsuperscript{123} However, superficial and deep closure techniques combined have not been studied yet, nor have the effect of using vacuum dressings in the early post-surgical course and the technique of wound closure to prevent PJI.

**Should tranexamic acid be standardly applied to patients who receive joint arthroplasty in order to prevent prolonged wound leakage and PJI?**

Tranexamic acid is an antifibrinolytic agent that reduces blood loss during and after joint arthroplasty. It is proven to be safe and can effectively reduce
the need for blood transfusions. Reducing blood loss should hypothetically result in less hematoma formation, which reduces the risk of PJI, but the effect of tranexamic acid on wound leakage and PJI has not yet been studied.

**Conclusion**

Although some research questions regarding risk factors and treatment strategies in early PJI were answered in this thesis, an important one remains unsolved: the optimal treatment of prolonged wound leakage after TKA/THA. Even though the results of the LEAK study are not available yet, we believe that these can provide important insights toward future treatment protocols for prolonged wound leakage. Coordinating the LEAK study has evidenced the challenge of performing large-scale randomized controlled trials. With the development of collaboration in CORE this may become easier in the future.

In terms of the risk factors for PJI, the studies in this thesis described that obese patients, oncology patients and patients with wound leakage are at an increased risk of developing PJI, drawing the following conclusions: 1) Antibiotic prophylaxis regimens should be adapted to reduce this risk of periprosthetic hip infections in obese patients. 2) Many aspects of the topic of oncologic PJI require additional research. Regarding the treatment of PJI, the following conclusions can be drawn based on this thesis: 1) The KLIC score can be used to estimate the risk of treatment failure after DAIR, although a risk score with a higher accuracy should be developed. 2) Application of gentamicin-impregnated beads and sponges should be discontinued in patients with early PJI undergoing a DAIR procedure. 3) DAIR is still a viable treatment option when patients with PJI present more than four weeks after index arthroplasty.
References

12. European committee on antimicrobial susceptibility testing. Data from the EUCAST MIC distribution website. www.eucast.org.
Chapter 10


General discussion and future perspectives


General discussion and future perspectives


