Periprosthetic Joint Infections

Advances in diagnosis, treatment and outcome

Jesse W.P. Kuiper

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The work presented in this thesis was performed at the Centre for Orthopaedic Research Alkmaar (CORAL), Noordwest Ziekenhuisgroep, Alkmaar, the Netherlands, the department of orthopedic surgery, Spaarne Gasthuis, Hoofddorp, the Netherlands, the department of oral cell biology and department of preventive dentistry, Academic Centre for Dentistry Amsterdam (ACTA), Amsterdam, the Netherlands, and the department of orthopedic surgery, VU University Medical Centre, Amsterdam, the Netherlands.

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Advances in diagnosis, treatment and outcome

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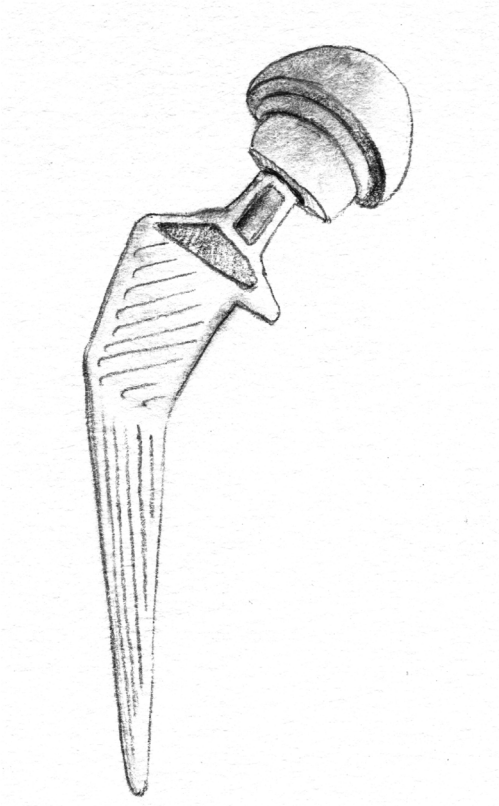
TABLE OF CONTENTS

CHAPTER 1

General introduction



CHAPTER 1 General introduction

Periprosthetic joint infection, or PJI is possibly the most debilitating complication of arthroplasty surgery, occurring in approximately 1% of patients who underwent hip or knee arthroplasty in the first years following surgery[1–3]. On the long term, PJI affects up to 2% of all patients[4,5]. The severity of PJI is expressed in increasing health care costs and consumption of hospital resources[6,7]. One can imagine the burden for the patient is immense: often, after surgery and weeks of antibiotic treatment, it is still possible that the new hip or knee needs to be removed to fully eradicate the infection[8]. Thus, adding to the investment of time and pain, this uncertainty is something most patients find difficult to handle. However, clinical studies on patient burden are scarce, with only a few studies reporting a lower quality of life (QoL) for the period between arthroplasty removal and reimplantation[9–12].

PJI diagnosis and treatment are hot topics, that have been studied extensively in the last years. Unfortunately, randomized controlled trials or even comparative studies between different treatment methods are difficult to perform because of the relatively low number of PJI. Most knowledge derives from (retrospective and prospective) cohort studies and meta-analyses of these studies. However, knowledge regarding PJI diagnosis and treatment has substantially moved forward in the last years, due to worldwide consensus meetings and unified guidelines, but also due to the considerable increase in published studies (Figure 1).

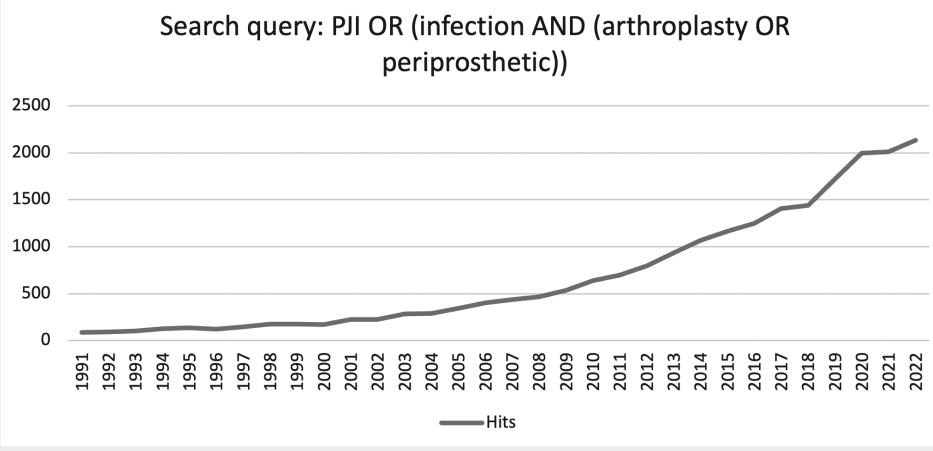


Figure 1: Number of hits on PubMed, per year, for publications on PJI (periprosthetic joint infection) (1991-2022).

Diagnosis and definition

In contrast to the clarity of the burden PJI causes, the diagnosis can sometimes be difficult to make. In cases of acute PJI, patients tend to have pain, swelling, wound leakage,

fever and even sepsis. However, such obvious symptoms of infection are just as often absent, and patients can present years after the initial arthroplasty with increasing pain, or, even vaguer, a decrease in function. Differentiating between aseptic loosening (with a non-infectious origin) and septic loosening (caused by PJI) can be difficult. In fact, a significant proportion of 'aseptic loosening' revisions may be (low-grade) infected[13].
In the early days of PJI studies, the diagnosis was usually made if multiple culture results were positive, or when pus was found during surgery[14]. This changed in the late nineties, when authors acknowledged the underestimation of PJI numbers with this method. Positive histopathology and the presence of a sinus tract were included in the criteria used for diagnosis[15], and sonication of the prosthesis became one of the possibilities to increase culture yield[16]. In 2011 a new definition was published by the Musculoskeletal Infection Society (MSIS criteria), and was adopted as a standard by the majority of authors in the following years[17]. In 2014, after the first worldwide consensus meeting on orthopedic infections, these criteria were renewed[18]. Recently, a criteria system using cumulative points was developed and validated[19]. Subsequently, these criteria were modified at the second international consensus meeting (ICM)[20]. See Table 1 for these latest, modified ICM 2018 criteria.
In 2017, the European Bone and Joint Infection Society (EBJIS) adapted another definition for PJI, that was developed in Switzerland, because a number of low-grade PJI are possibly missed using the MSIS criteria[21]. In 2021, the EBJIS published a new classification system, allocating patients to three groups: *infection unlikely*, *infection likely*, and *infection confirmed*[22]. See Figure 2 for the 2021 EBJIS classification.

Major criteria (at least one of the following):		
Two positive cultures of the same organism Sinus tract with evidence of communication to the joint or visualization of the prosthesis		**Infected**

Preoperative score: minor criteria	**Score**	**Decision**
Serum: elevated CRP *or* D-Dimer	2	≥6: infected 2-5: possibly infected* 0-1: not infected
Serum: elevated ESR	1	
Synovial: elevated synovial WBC count *or* LE	3	
Synovial: positive alpha-defensin	3	
Synovial: elevated synovial PMN (%)	2	
Synovial: elevated synovial CRP	1	

Intraoperative score: minor criteria (Inconclusive preoperative score* *or* dry tap)	**Score**	**Decision**
Preoperative score	-	≥6: infected 4-5: inconclusive 0-3: not infected
Positive histology	3	
Positive purulence	3	
Single positive culture	2	

Table 1: PJI (periprosthetic joint infection) scoring system, as agreed upon by consensus at the International Consensus Meeting 2018 in Philadelphia (ICM 2018 criteria)[20]; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; WBC: white blood cell count; PMN: polymorphonuclear neutrophils.

	Infection Unlikely (all findings negative)	Infection Likely (two positive findings)[a]	Infection Confirmed (any positive finding)
Clinical features	Clear alternative reason for implant dysfunction (e.g., fracture, implant breakage, malposition, tumor)	1) Radiological signs of loosening within the first five years after implantation 2) Previous wound healing problems 3) History of recent fever or bacteremia 4) Purulence around the prosthesis[b]	Sinus tract with evidence of communication to the joint or visualization of the prosthesis
Serum C-reactive protein		> 10 mg/l (1 mg/dl)[c]	
Synovial leukocyte count[c] (cells/µl)	≤ 1,500	> 1,500	> 3,000
PMN (%)[c]	≤ 65%	> 65%	> 80%
Alpha-defensin[e]			Positive immunoassay or lateral flow assay[e]
Aspiration fluid cultures[f]		Positive culture of aspiration fluid	
Intraoperative cultures (fluid and tissue)[f]	All cultures negative	Single positive culture[g]	≥ two positive samples with the same microorganism
Sonication cultures[f,h] (CFU/ml)	No growth	> 1 CFU/ml of any organism[g]	> 50 CFU/ml of any organism
Histology[c,i] in high-power field (400x magnification)	Negative	Presence of ≥ five neutrophils in a single HPF	Presence of ≥ five neutrophils in ≥ five HPF or presence of visible microorganisms
Nuclear imaging	Negative three-phase isotope bone scan[c]	Positive WBC scintigraphy[j]	

Table 2: The 2021 EBJIS (European Bone and Joint Infection Society) criteria for PJI (periprosthetic joint infection)[22]; PMN: polymorphonuclear neutrophils; CFU: colony forming units; HPF: high power fields.

Microorganisms

PJI are usually caused by gram-positive, aerobic microorganisms: *Staphylococcus aureus* (27%), coagulase-negative *Staphylococcus* (CNS, 27%), *Streptococcus* species (8%) and *Enterococcus* species (3%)[23]. Other causative microorganisms are aerobic gram-negative bacilli (9%, e.g. *Escherichia coli*), anaerobic bacteria (4%, e.g. *Propionibacterium acnes*) and fungi (1%)[23,24]. In 14%, no causative microorganisms are found (culture-negative PJI), and multiple species are found in 15%[23]. Different species cause different symptoms: for example, *Staphylococcus aureus* infections are known for their acute onset with infections symptoms, and are known to spread to other joints and heart valves, whereas PJI caused by CNS usually has a more chronic profile[8].
The rise of multi-drug-resistant microorganisms such as methicillin resistant *Staphylococcus aureus* (MRSA) is a large concern, although more in the United States than in Europe[25]. However, if resistance keeps increasing, antibiotic treatment becomes more and more problematic[23].

Biofilm development

One of the reasons PJI can be difficult to treat, is the development of a biofilm on the arthroplasty components. The metal and polyethylene parts of a prosthetic joint are a foreign body and have no internal blood flow, and therefore no natural defense against microorganisms. Many bacterial species, when adhering to the surface of foreign bodies, immediately start producing a biofilm: a protective slime layer, consisting of polysaccharides, extracellular DNA and proteins. In the biofilm, bacteria are much more resistant to antibiotic treatment, due to decreased antibiotic penetration. Furthermore, other factors may play an even more important role: bacteria transform from their 'free', planktonic state to a less metabolically active, more dormant and much more resistant biofilm state. During the development, its biofilm 'matures', and curation becomes more difficult[26].
Without the biofilm, PJI (and other infections) would be much easier to treat, but as it is, most treatment methods are focused on the combination of physically removing the biofilm and prolonged antibiotic treatment using the most effective agents against biofilm microorganisms.

Treatment methods

Treatment of PJI has two pillars: drug treatment with antibiotic agents, and surgical treatment. Different methods are available for different bacteria, different clinical situations, and different types of PJI.
Acute infections are usually caused by highly virulent bacteria such as *Staphylococcus aureus*, and can occur in the period following the initial arthroplasty ('direct postoperative'), or years later with an acute onset, usually due to a *porte d'entrée* somewhere else ('acute hematogenous'). These PJI are usually treated with debridement, antibiotics, irrigation and implant retention (DAIR): the joint is reopened, thoroughly debrided (removal of all infected and necrotic tissue) and irrigated with saline, although some surgeons use antibiotics, povidone-iodine or other antimicrobial agents for irrigation. The parts of the prosthesis that are easily replaced are removed and new parts are inserted after the debridement and irrigation; a not too subtle way of removing (most of) the biofilm. After surgery, prolonged antibiotic treatment (usually 6 to 12 weeks) is recommended[8,27].
For chronic PJI (and after DAIR failure), all arthroplasty components are removed and replaced after extensive debridement, either during the same surgery session (one-stage revision), or weeks to months later (two-stage revision or staged revision)[8]. One-stage revision is performed less frequently than two-stage revision[28]. However, in selected, favorable cases (e.g. caused by a known, well treatable microorganism and good soft tissue coverage), success rates increase, and one-stage revision can be considered according to guidelines[8,29].

Thesis outline

The overall aim of this thesis was to advance knowledge of PJI in three separate subjects: diagnosis of PJI (Chapter 2 to 5), treatment of PJI (Chapter 6 to 10), and outcomes after PJI (Chapter 11 and 12). This aim was pursued by assessing current knowledge and practice, identifying and studying hiatuses in knowledge, and studying new tools and agents for better PJI diagnosis and treatment.

In Chapter 2, the results of a survey study are described, that was performed in the Netherlands and Belgium in 2013. All hospitals were approached to answer questions regarding the diagnosis and treatment of PJI. Roughly half of the hospitals responded, and interestingly, large intranational and international differences were seen between these two neighboring countries. Only a small part of respondents seemed to adhere to recent guidelines, at that time.

Chapter 3 is a meta-analysis including all prospective studies on the use of a new diagnostic tool, the alpha-defensin test, for hip and knee PJI. This test is available as an immunoassay-based laboratory test and as a point-of-care lateral flow test (not unlike a pregnancy test). Fifteen studies were included after a thorough search, four describing the immunoassay and eleven the lateral flow test. Both performed well, with a high sensitivity and very high specificity. By contacting authors for additional information, it was possible to perform a subgroup analysis for total hip arthroplasty (THA) versus total knee arthroplasty (TKA). Although only two studies were pooled for subgroup analysis of the immunoassay test, a lower sensitivity for PJI diagnosis in THA was found, compared to TKA. This was not found for the lateral flow test. Some explanations for this result are given in the chapter, plus the recommendation for authors to always describe different joints separately.

In Chapter 4, the results of a retrospective pilot study on the alpha-defensin (AD) lateral flow test for THA PJI are presented. In this pilot study with 52 patients, the lateral flow test was evaluated using the modified MSIS criteria (2014). In addition, the ICM 2018 and EBJIS (2018) definitions for PJI were used as well. The test performed well, with a sensitivity of 100% and specificity of 89% (modified MSIS criteria). Using the ICM 2018 criteria led to a sensitivity of 91% and specificity of 100%. When applying the EBJIS criteria, sensitivity was 71% and specificity 97%.

These results encouraged us to perform a prospective study of the AD lateral flow test for hip PJI, the results of which are described in Chapter 5. After including 57 patients, using the modified MSIS criteria, a sensitivity of 83% and specificity of 92% were found. A slightly smaller group of patients did not undergo revision surgery and was therefore excluded from the analysis, but should not be forgotten. In these “Schröding-er’s hips”, as we dubbed them, PJI can neither be confirmed nor excluded, and they should therefore be described as a second arm in future studies.

In Chapter 6, the results of an in vitro study are presented, assessing the effect and safety of XZ.700, an endolysin specifically targeting the *Staphylococcus aureus* cell wall. Two models were used, a static and a dynamic model. XZ.700 showed good results in the static model, and did very well in the dynamic model, better than povi-

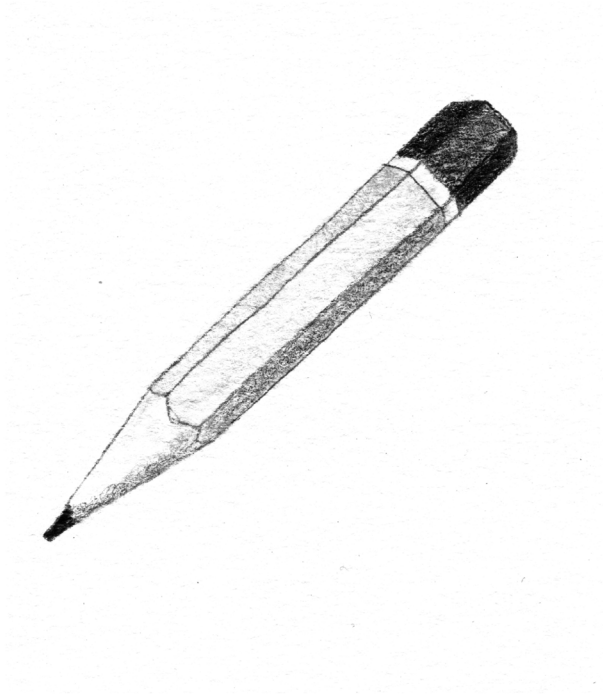
done-iodine and gentamicin, two currently used topical treatment agents. XZ.700 also showed no toxicity on human osteocyte-like cells.
Chapter 7 is a summary of acute PJI diagnosis and treatment. Debridement, antibiotics, irrigation and implant retention (DAIR) is the primary treatment for acute PJI, and success rates of 60-80% have been described in most studies. It remains unclear whether a strategy of single DAIR or of multiple DAIR procedures have a higher infection eradication rate. In different studies, different factors have been described to contribute to treatment failure, of which longer duration of symptoms, longer time after initial arthroplasty, the need for more debridement procedures, the retention of exchangeable components, and PJI caused by *Staphylococcus* (*aureus* or coagulase negative) may be the most important.
In Chapter 8, a retrospective cohort study is presented, on the local application of resorbable gentamicin sponges after DAIR in 34 patients with hip PJI. A success rate of 70% was found, with a mean follow-up of 35 months. Four patients had temporary renal insufficiency during the treatment period, but their creatinine values returned to preoperative values afterwards, and no permanent complications were seen. Although the cohort was small, symptom duration of more than four weeks was significantly associated with treatment failure. The success rate of 70% was in concordance with other studies on DAIR, although no other studies described the use of gentamicin sponges.
In a multicenter retrospective cohort study that was performed in Alkmaar, Hoofddorp and Amsterdam, 91 patients were treated with DAIR for hip or knee PJI, with a mean follow-up of three years (Chapter 9). Success was achieved in 66% of all cases. An association with treatment failure was found for several factors: history of rheumatoid arthritis, late infection (more than two years after initial surgery), erythrocyte sedimentation rate (ESR) higher than 60 mm/hour at presentation, symptom duration of more than one week, and when coagulase-negative *Staphylococcus* was found in cultures.
Chapter 10 is a review on the treatment of fungal PJI. After searching and selecting the literature, 64 studies were included. With the addition of eight patients from our own institutions, 164 patients were treated for fungal PJI, most of which were *Candida* infections (88%). Of 119 patients with a follow-up longer than two years, 79 were treated with two-stage revision, with 85% infection eradication. The patients that underwent two-stage revision had the highest success rate, compared to DAIR (4/22, 18%), one-stage revision (1/2, 50%), and antifungal therapy alone (0/3, 0%). In conclusion, fungal PJI resembles chronic bacterial PJI, and two-stage revision should be the gold standard of treatment.
The results of a systematic review on the effect of two-stage revision for hip PJI on the (health related) quality of life (or (HR)QoL) are presented in Chapter 11. For one-stage revision, no studies were found. For two-stage revision, twelve studies were included, with moderate study quality overall. QoL scores presented were the HOOS (Hip disability and Osteoarthritis Outcome Score), WOMAC (Western Ontario and McMaster Universities Osteoarthritis Index) and SF-12 and -36 (Short Form 12 and Short Form 36). (HR)QoL after two-stage revision, although lower than in the general population, was comparable to (HR)QoL after aseptic revision.

In Chapter 12, a cohort of 30 patients is described that underwent one-stage revision for hip PJI. Patient related outcome measures for functional outcome (HOOS and Oxford Hip Score) and QoL (EuroQoL 5 Dimensions Questionnaire, EQ-5D) were assessed. After follow-up (minimum one year), 93% did not have relapse or reinfection. The functional outcome and QoL scores were high, comparable to scores after revision arthroplasty in general.
After these chapters, the problems that we currently face and what we should do about them in the future are discussed.

DIAGNOSIS
OF PERIPROSTHETIC JOINT INFECTIONS

CHAPTER 2

Variety in diagnosis and treatment of periprosthetic joint infections in Belgium and the Netherlands



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CHAPTER 2

Variety in diagnosis and treatment of periprosthetic joint infections in Belgium and the Netherlands

Abstract

Recently, guidelines regarding diagnosis and treatment of periprosthetic joint infection (PJI) have been published, but it is unknown how well these are followed in the Netherlands and Belgium. Therefore, a survey study was performed in the Netherlands and Belgium. 81 Orthopedic departments responded (54% in the Netherlands, 52% in Belgium). The majority used protocols for antibiotic and surgical treatment. To discriminate between early and late infection, differences in periods used were seen between respondents, and between countries. Empirical antibiotic treatment varied greatly. Debridement, antibiotics, irrigation and implant retention (DAIR) is the almost unanimous treatment of choice for early PJI. Guidelines are available, but seem not (yet) to be followed accurately, and do not have answers to all possible treatment options. Perhaps, national guidelines might produce more standardized care, and consequentially, easier comparison for research, more transparency for patients, and less health care costs.

Introduction

With the absolute increase in total hip arthroplasty (THA) and total knee arthroplasty (TKA) performed each year[6], a rise in (absolute) number of complications can be expected. Of these, periprosthetic joint infection (PJI) is one of the most devastating complications. Whether the treatment consists of chronic antibiotic use, multiple debridement procedures, one or twostage revision or even a Girdlestone procedure, long term hospital stay and surgery are required in most cases[8]orthopedists, and other healthcare professionals who care for patients with prosthetic joint infection (PJI. According to the National Institute for Public Health and the Environment in the Netherlands[30], in 2013 approximately 100.000 THA and 70.000 TKA were performed. With a PJI rate of 1.8 and 1.3%, respectively, a total number of around 2700 hip and knee PJI were seen. When also counting infections of revision knee and hip arthroplasty and hip hemi-arthroplasty, this adds up to approximately 3700 PJI, yearly, in the Netherlands. Revision arthroplasty for PJI costs around 30.000 euro per patient for THA[6,31], and around 25.000 euro per patient for TKA[6]. So, in the Netherlands alone, the total costs of knee and hip PJI are approximately 100 million euro yearly. Therefore, treatment should be optimized, thus minimizing total costs[31]. To optimize treatment, the best possible evidence needs to be made public, for example by (national/international) guidelines. Plus, standardization would also aid comparison of different treatment options. Just until recently, the first real guidelines have been published[8]orthopedists, and other healthcare professionals who care for patients with prosthetic joint infection (PJI, and soon the results of international efforts to reach consensus will be made public. Still, as it is seen more often in health

care, we believe that these advices have not yet transuded to hospital protocols and individual doctors. To test this hypothesis, and to raise awareness for treating patients with PJI with the best evidence-based medicine, a survey study was performed.

Methods

In March 2013 a survey regarding the treatment of PJI was sent to all orthopedic departments in the Netherlands and Belgium. A total of 152 orthopedic surgery departments in the Netherlands and Belgium were contacted. In the following months, all departments that had not responded were asked again twice to respond, first by email, and secondly by a telephone call. The survey was an online questionnaire, and could be completed within 1015 minutes. It was designed by the leading author, and after redaction by all other authors agreed upon and published. It was divided in three parts: demographics and protocols, diagnostics, and antibiotic and surgical treatment, all of which contained approximately 10 questions. For most questions, an “other” box was added, for free text. In Table 1 the questions are listed.

Demographics and protocols
Type of hospital
Number of THA performed in 2012
Number of TKA performed in 2012
Number of hip PJI in 2012
Number of knee PJI in 2012
Percentage of PJI referred to your hospital by others
Multidisciplinary meeting for PJI treatment
Is a set protocol used for antibiotic treatment of PJI?
Is a set protocol used for surgical PJI treatment?
Diagnostics and antibiotic treatment
Diagnostic tools used for PJI diagnosis
Where is aspiration performed in case of suspected hip PJI?
Where is aspiration performed in case of suspected knee PJI?
What threshold is used to discriminate between early and late PJI?
Which antibiotic agent is used for empirical therapy (when the causative microorganism is yet unknown)?
Is additional rifampin added to therapy?
Is the antibiotic therapy changed according to culture results?
What is the minimal total period of antibiotic treatment?
Surgical treatment
What kind of surgical treatment is performed for early PJI?
What kind of surgical treatment is performed for late PJI?
Is a set criterion used to choose between DAIR and implant removal?
Is a set number of DAIR procedures used?
If any, what local antibiotic treatment is used in DAIR procedures?
Are exchangeable components always exchanged?
If any, what local antibiotic treatment is used in implant removal surgery?
What period is used between removal and reimplantation in staged revision?

Table 1: Questions asked in the 2013 survey regarding the treatment of PJI (periprosthetic joint infection), that was sent to all orthopedic departments in the Netherlands and Belgium; THA: total hip arthroplasty; TKA: total knee arthroplasty; DAIR: debridement, antibiotics, irrigation and implant retention.

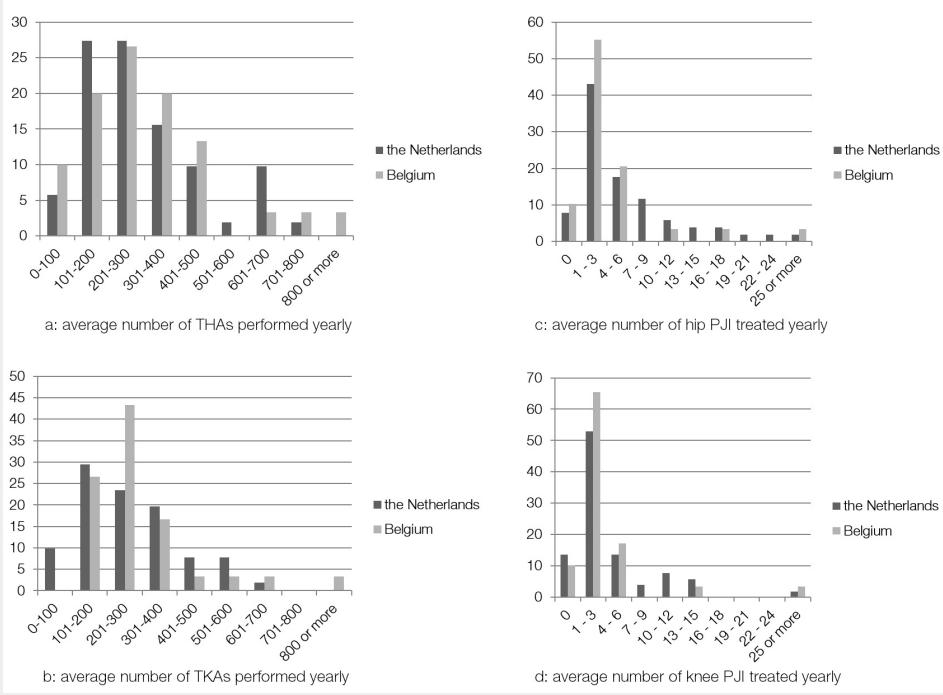

Figure 1a-d: Demographics (in percentages) of the respondents, in annual number of total hip arthroplasties (THA) (1a), total knee arthroplasties (TKA) (1b), hip periprosthetic joint infection (PJI) (1c) and knee PJI (1d).

Results

In total, 81 orthopedic departments responded to the survey: 51 in the Netherlands (54% response), and 30 in Belgium (52%). Of the Dutch responses, 44% were from teaching hospitals (17% university hospitals), versus 86% in Belgium (6% university hospitals). Per year, most Dutch hospitals perform between 101 and 400 THA and TKA (71% and 73%, respectively). In Belgium, between 101 and 400 THA and TKA are performed in 67% and 87% of the hospitals, respectively. The most hospitals treat 13 hip and knee PJI on a yearly base. The number of THA and TKA, as well as the number of infections are shown in Figure 1.

When asked for the percentage of PJI patients that are referred to the responding surgeon, the largest group have few referrals: 44% of the Dutch, and 28% of the Belgian respondents have <10% referred patients. The second largest group, however, have 90-100% referred patients: 16% and 17%, respectively.
A multidisciplinary approach for PJI treatment is standard care in 55% of the Dutch hospitals and 33% of the Belgian hospitals. In both countries, this usually involves a medical microbiologist. Protocols for antibiotic and surgical treatment do exist in most

	the Netherlands	Belgium
Multidisciplinary approach		
None	38%	47%
With a microbiologist	35%	19%
With an infectiologist	2%	6%
With both	16%	3%
Other	2%	6%
No answer	7%	19%
Use of protocol		
Regarding the use of antibiotics	87%	76%
Regarding surgical treatments	77%	59%

Table 2: Percentages of multidisciplinary and standardized care for treatment of periprosthetic joint infection in the Netherlands and Belgium.

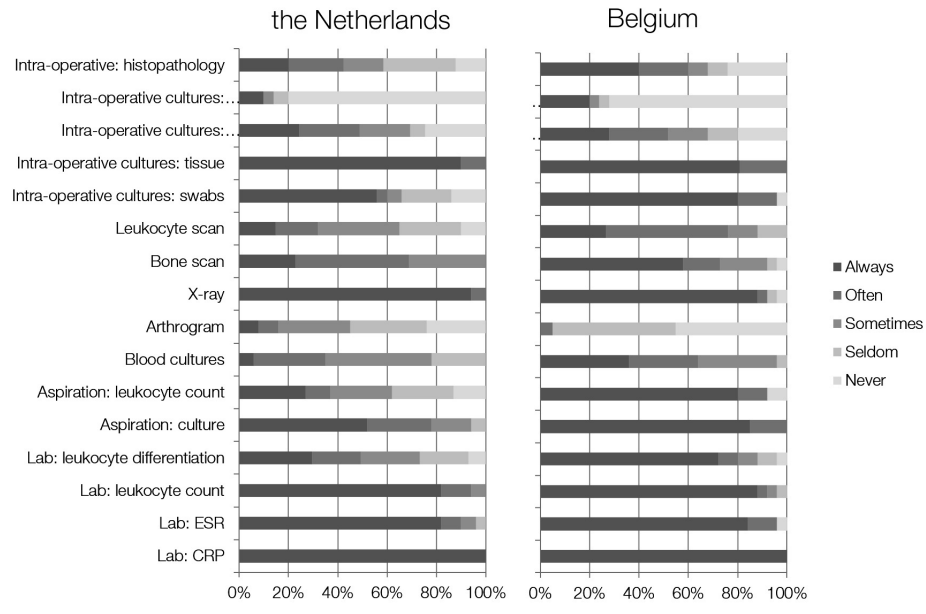

Figure 2: Diagnostic methods used for diagnosis of periprosthetic joint infection, in percentages; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein.

hospitals, slightly more in the Netherlands. Here, antibiotic and surgical treatment is standardized in 87% and 77% of the hospitals, versus 76% and 59% in Belgium, respectively (Table 2).

The use of possible methods to diagnose PJI are listed in Figure 2. Creactive protein (CRP), erythrocyte sedimentation rate (ESR), leukocyte count, X-ray, and intraoperative tissue cultures are almost always performed in both countries (more than 80% responded “always”). In Belgium, intraoperative swab cultures, aspiration leukocyte count, aspiration culture and serum leukocyte count are also almost always performed, which is

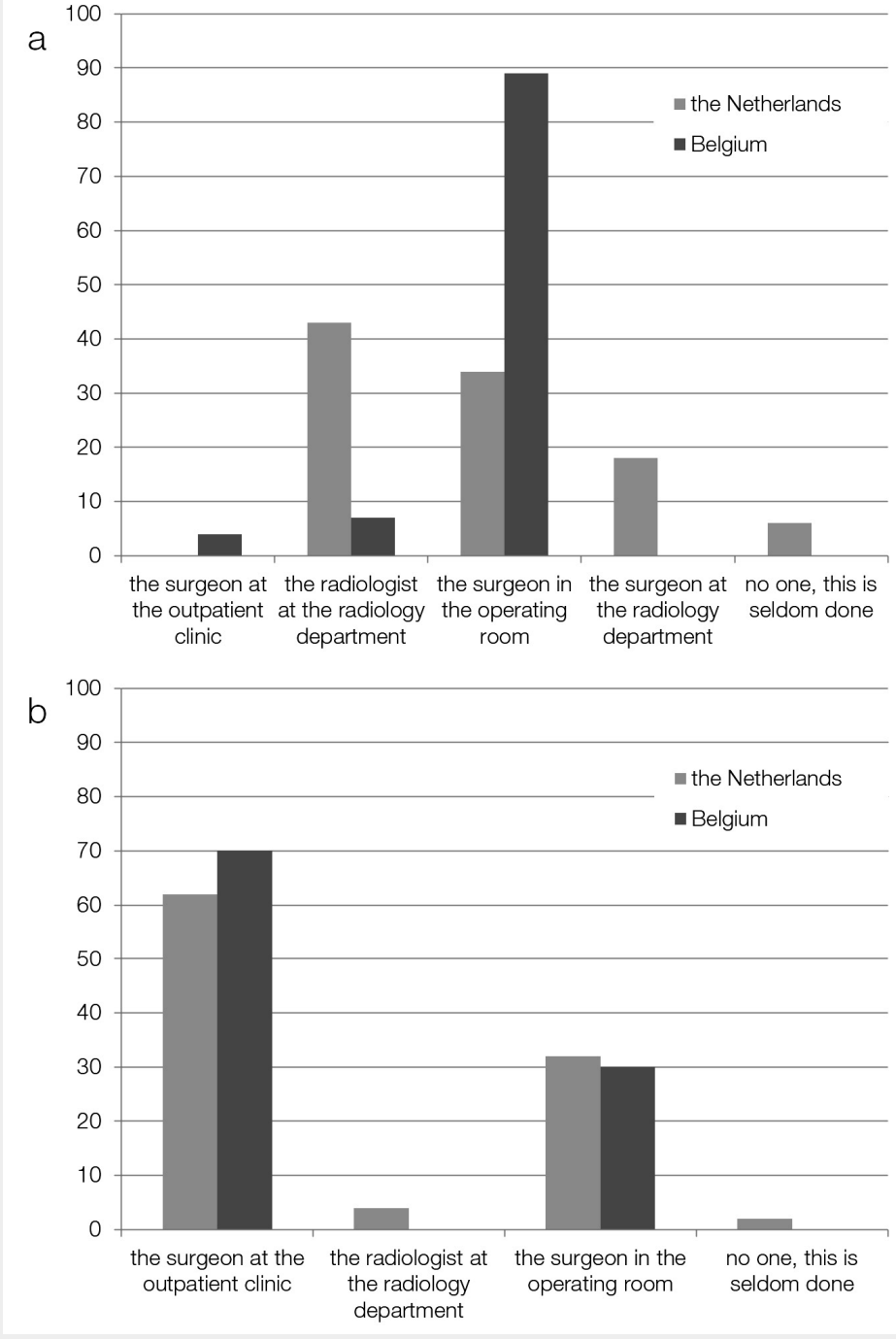

Figure 3a and 3b: Methods of sterile joint aspiration of the hip (3a) and knee (3b) for diagnosis of periprosthetic joint infection, in percentages.

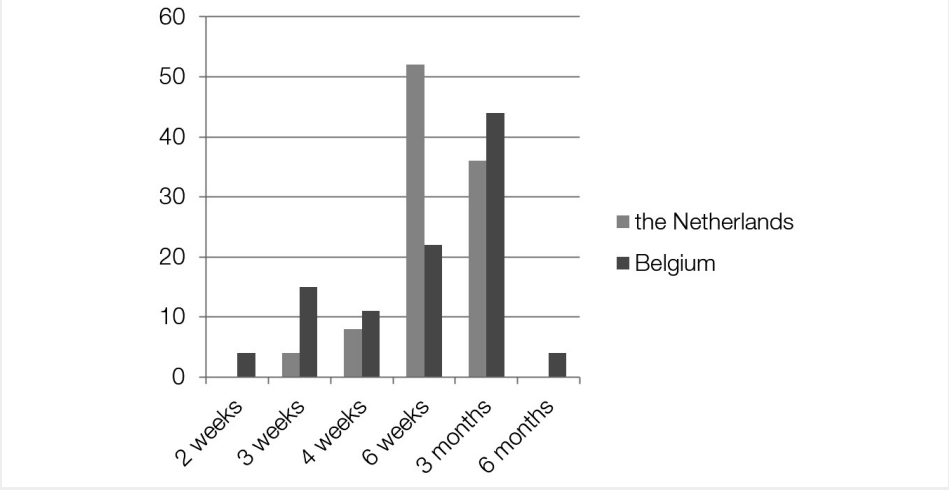

Figure 4: Threshold used for early versus late periprosthetic joint infection, in percentages.

less in the Netherlands. Arthrography is almost never performed in Belgium, but sometimes in the Netherlands. Sonication of prosthetic material is either always performed (10% in the Netherlands, 20% in Belgium), or not at all (80% and 70%, respectively).

For PJI diagnosis, almost every hospital performs standard joint aspiration. A difference between the countries is seen regarding suspected hip PJI. In Belgium, aspiration is almost always performed in the operating room. In the Netherlands, this is also done at the radiology department by either a radiologist or orthopedic surgeon. When knee PJI is suspected, two thirds of the patients are aspirated at the outpatient clinic, and one third in the operating room. This is the same in both countries (Figure 3).

Only few hospitals always perform all the tests that are mentioned in the definition of PJI diagnosis: only 6% of the Dutch and 18% of the Belgian respondents always perform CRP, ESR, aspiration leukocyte count, cultures and histology[18].
When asked for a threshold to discriminate between early and late infection, more than half of the Dutch respondents use six weeks postoperatively, and another 36% three months. In Belgium, this is spread out between 2 weeks and six months, with a peak at three months (44%) (Figure 4).

Antibiotic treatment differs between the two countries. In Belgium, as empirical treatment, mostly amoxicillin/clavulanate or a combination of agents is given (21% and 31%, respectively), whereas in the Netherlands flucloxacillin and cephalosporins are more commonly used (28% and 36%, respectively). Adjuvant therapy with rifampin is frequently used in the Netherlands, and seems a bit less used in Belgium. Adaptation of the antibiotic regiment is always done in consultation, usually after consulting the microbiologist (Table 3).

Empirical antibiotic treatment*	the Netherlands	Belgium
Amoxicillin/clavulanate	8	21
Flucloxacillin	28	10
Vancomycin	6	10
Cefuroxime	18	0
Cefazolin	14	7
Ceftriaxone	4	0
Clindamycin	4	0
Ciprofloxacin	2	0
Amikacin	0	3
Combination therapy	10	31
Flucloxacillin/vancomycin	*4*	*3*
Ciprofloxacin/vancomycin	*2*	*0*
Gentamicin/vancomycin	*2*	*0*
Amikacin/vancomycin	*2*	*0*
Flucloxacillin/gentamicin	*0*	*10*
Flucloxacillin/amikacin	*0*	*7*
Cefazolin/ciprofloxacin	*0*	*3*
Cefazolin/amikacin	*0*	*3*
Clindamycin/ciprofloxacin	*0*	*3*
In consultation with a microbiologist	6	10
“Broad spectrum”	0	3
Cephalosporins	0	3
Rifampin use		
Always	12	3
Often	31	17
Sometimes	10	41
Seldom	3	7
Never	2	0
Later, based on culture results	26	21
Other	16	10
Adaptation of antibiotic treatment based on culture results		
Use of a set protocol	0	0
In consultation with a medical microbiologist	86	78
In consultation with an infectiologist	2	15
In consultation with both	12	7
Without consultation	0	0
No adaptation	0	0
Other	0	0

Table 3: Use of antibiotic agents in PJI treatment, in percentages; *: with or without the use of rifampin.

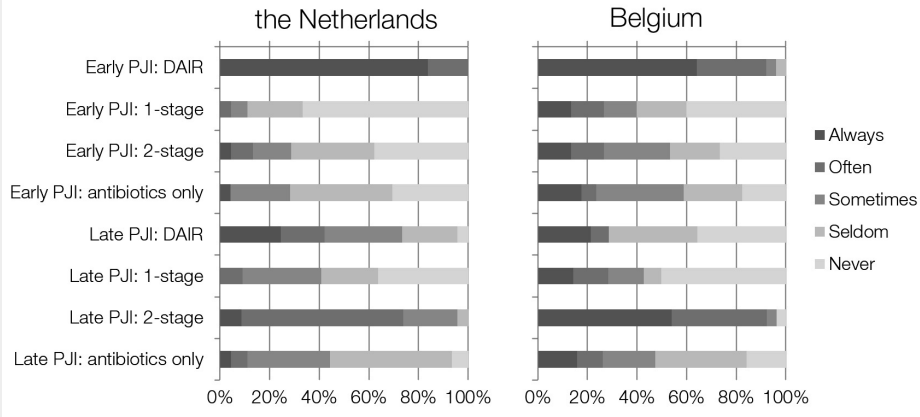

Figure 5: Treatment methods used for early and late periprosthetic joint infection (PJI), in percentages; DAIR: debridement, antibiotics, irrigation and implant retention.

Is a fixed number of DAIR procedures used?	The Netherlands	Belgium
Yes, 1	2%	12%
Yes, 2	4%	0%
Yes, 3	2%	0%
No, 1 or 2 (maximum 2)	18%	8%
No, 1, 2 or 3 (maximum 3)	22%	12%
No, 1, 2, 3 or 4 (maximum 4)	2%	0%
No, 1, 2, 3, 4 or 5 (maximum 5)	2%	0%
No, but a maximum is used (number not given)	2%	4%
No, this is guided by negative cultures after the last procedure	6%	0%
No, this is guided by negative cultures after the 2 last procedures	2%	0%
No, this is guided by negative cultures (number of times not mentioned)	6%	12%
No (not further specified)	31%	54%

Table 4: Fixed number of procedures used or not used when debridement, antibiotics, irrigation and implant retention (DAIR) is performed, in percentages.

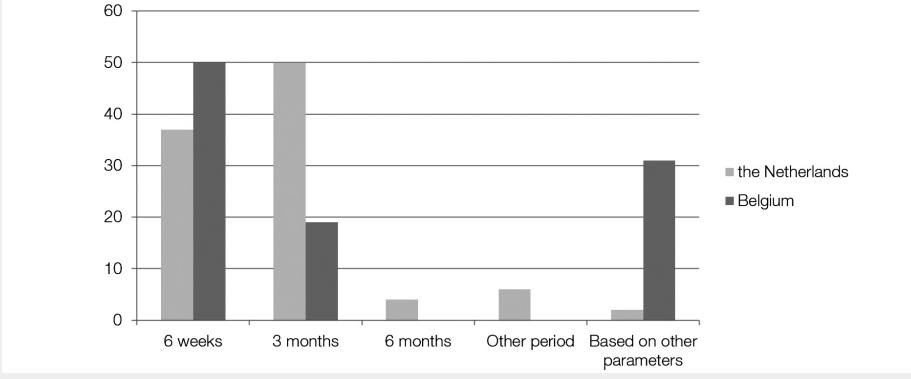

Figure 6: Minimum period until reimplantation is performed after removal surgery for periprosthetic joint infection, in percentages.

Early PJI are almost always treated with debridement, antibiotics, irrigation and implant retention (DAIR) in both countries. Onestage revision, twostage revision and the (chronic) use of antibiotics only are far less used. Remarkably, treatment with antibiotics only is still used in around 15% of all cases of both early and late PJI in Belgium. In the Netherlands, this is much less used, approximately 5%. The same kinds of results are shown for one and twostage revision for early PJI: 15% in Belgium, 5% in the Netherlands.
For late PJI, twostage revision is most frequently used, but in a substantial part DAIR is also tried (always or often in 40% in the Netherlands, and 20% in Belgium). Onestage revision and antibiotics only seem less favorite in both countries, and are more or less equally used for early and late PJI (Figure 5).

In most hospitals, the criterion to choose between DAIR and removal of the prosthesis for one or twostage revision is not well-defined, and a personal choice for each patient (based on different clinical symptoms) is made by approximately half of the respondents (50% in the Netherlands, 44% in Belgium). Other hospitals are more strict in their decision and use a selected time after primary surgery (25 and 37%, respectively), symptom duration (6 and 7%, respectively), loosening of the prosthesis (6 and 3%, respectively), or "other reasons", usually a combination of the previous mentioned reasons (13 and 7%, respectively).
If DAIR is performed, the number of DAIR procedures attempted varies significantly between respondents. A fixed number (either always one, always two or always three procedures) is used by the minority in the Netherlands. In Belgium, on the contrary, a fixed number is used by 12%, but this is always one try. When a variable number of procedures is used, 46% of the Dutch respondents and 24% of the Belgians wield a maximum number of DAIR procedures, usually 2 or 3 attempts. Some hospitals are guided by the negative cultures found in the previous procedure(s) (12 and 14%, respectively).
The exchange of modular components during DAIR procedure is much higher in Belgium (77% always, 15% sometimes) than in the Netherlands (41% always, 35% sometimes).
For DAIR treatment, local antibiotic carriers are used by 88% of the Dutch, and 73% of the Belgium respondents. In both countries, 38% of the respondents use an antiseptic or antibiotic agent for irrigation. After prosthesis removal, beads and sponges are more frequently used in the Netherlands, whereas the Belgians obviously prefer spacers (Table 4).

After removal of the prosthesis, the interval period used before reimplantation differs between the two countries: the Dutch use either six weeks or three months in most hospitals, the Belgian respondents use six weeks in half of the hospitals, but a third based this on other parameters, such as serum infection protein levels and clinical symptoms (Figure 6).

Discussion

Although the most respondents state to use a standardized treatment protocol, for both the medical and surgical treatment of PJI, the answers to most questions are not unam-

biguously. For such a severe complication, treatment should be optimal for each patient, and according to the latest evidence. Unfortunately, the evidence for many diagnostic tools and treatment options is poor and uncertain; for diagnosis and surgical treatment, no randomized controlled trials exist, and only a few exist for antibiotic treatment[8].
For PJI diagnosis, the IDSA guideline mentions the utility of ESR, CRP, X-ray, preoperative aspiration, blood cultures, intraoperative histology and intraoperative cultures[8]. Of these 7 test methods, 3 are not routinely used in both countries: aspiration (especially in the Netherlands), blood cultures and histology. Only a minority of the respondents perform all tests to possibly fulfil these minor criteria (6% in the Netherlands, 18% in Belgium).
The latest criteria for PJI diagnosis, as agreed upon during the 2013 consensus meeting, are as follows[18]:

- Two positive periprosthetic cultures with phenotypically identical organisms, or
- A sinus tract communicating with the joint, or
- Having three of the following minor criteria:
    - Elevated serum C-reactive protein (CRP) AND erythrocyte sedimentation rate (ESR)
    - Elevated synovial fluid white blood cell
    - (WBC) count OR ++ change on leukocyte esterase test strip
    - Elevated synovial fluid polymorphonuclear neutrophil percentage (PMN%)
    - Positive histological analysis of periprosthetic tissue
    - A single positive culture

The use of additional imaging (bone scan, leukocyte scan) has only a limited role in PJI diagnosis[8,18], but it is used “always” by 15-55% of the respondents.
Location and performing physician of joint aspiration (arthrocentesis) differs between the countries and the affected joints. The most optimal way to perform aspiration for PJI diagnosis is not mentioned by other authors, but perhaps this is less relevant than the most important issue: it should be as sterile as possible, and true joint fluid should be aspirated.
A big difference is seen in the threshold surgeons wield between early and late infection between the two countries, but also between the respondents. Of course, the different classification systems play a role in this difference: Tsukayama *et al.* described 4 postoperative weeks, Toms *et al.* adapted this to 6 weeks, and the Zimmerli classification uses 3 months[14,32,33]. Additionally, to choose between DAIR treatment or implant removal, the IDSA guidelines advise a threshold of 30 days or 3 weeks of PJI symptoms[8].
The Belgians tend towards a 3 months threshold between early and late PJI. The Dutch, on average, use a shorter period (more claim to use 6 weeks). The reason of this difference is difficult to ascertain. Perhaps the Zimmerli classification is used more often in Belgium[33]. Whether the difference has a clinical consequence and affects patient outcome is unknown.

Empirical antibiotic treatment differs extremely between respondents. In the Netherlands, there is a tendency to use smaller spectrum antibiotic agents (e.g., flucloxacillin instead of amoxicillin/clavulanate). This may be because the Netherlands are known for their low antibiotic subscription rate[34]. No advice is given in current guidelines[8], but one Portuguese study advises the use of vancomycin for PJI caused by an unknown microorganism[35]. In our population, vancomycin was used by 1316% of the respondents, either alone or in combination.
The additional use of rifampicin is more widely studied and recommended by most[8,33], at least when not all foreign material is removed. The answers of the respondents vary, but this may be due to the fact that we did not differentiate between prosthesis retention and removal.

Although the definition of early PJI is variable, almost all respondents treat this kind of infection with DAIR. The number of DAIR procedures that is attempted before removal is considered is widely variable, but the Dutch seem to perform more procedures than the Belgians. The number of procedures is not mentioned in the IDSA guidelines[8], but various studies state that one debridement procedure with additional procedures on indication seem to have a slightly higher success rate[36–38]. Others claim that standard multiple procedures perform better[39,40].
Of the respondents, 1214% are guided by negative cultures found in the previous procedure(s) to decide whether a next debridement procedure should be performed. This approach is not mentioned in guidelines or reviews[8,33], and to our knowledge, no evidence exists that this should be a factor in treatment choice.
Deciding performing either DAIR or removal (for one or twostage revision) is not well defined, and depends on several different factors, such as time after initial arthroplasty, symptom duration and prosthesis loosening[8,33]. However, the majority makes a weighted decision for each individual patient.
The exchange of modular components is more commonly performed in Belgium than in the Netherlands. Nevertheless, there are still respondents in both countries that do not always exchange components after debridement and irrigation. Several studies have shown that retention of these parts has worse outcome[41,42], and the IDSA guidelines advise against it[8].
The use of local antibiotic treatment is relatively common in the Netherlands and Belgium (88% and 73%). The evidence for or against local treatment is poor, and the choice of local carrier seems debatable; beads have a longer lasting but lower concentration of antibiotics, and can become a carrier of microorganisms themselves[43]. Sponges reach a higher concentration in a shorter period, and do not need removal surgery, but may cause more wound secretion[44].

For late PJI, twostage revision is performed the most. Onestage has as smaller, but significant role in both countries. Why onestage revision was sometimes chosen over twostage was not asked, but this may be based on preference of the performing surgeon.
In both countries, DAIR is performed for late PJI as well. Results after DAIR treatment

for late chronic PJI are poor, but for acute hematogenous PJI, which can occur up to years after initial arthroplasty, the results may be good[27].
As for local antibiotic treatment after prosthesis removal, many options were mentioned. In Belgium, most respondents use spacers, while the Dutch seem to use all options mentioned about equally (spacers, beads, sponges). The use of spacers may cause less functional problems for the patient, but this is not well studied[8].
The minimum period until reimplantation is usually at least 6 weeks, and the Dutch seem to use at least 3 months in most cases. To our knowledge, no evidence exists to support either period.
Regarding the use of antibiotic agents, the guidelines advise 46 weeks of antibiotic treatment, and subsequently 28 extra weeks without antibiotic[8]. It is also advised to use clinical parameters such as CRP to guide the reimplantation period[8], something that seems to be used more in Belgium than in the Netherlands.

This study clearly indicates the variety of diagnostic options and treatments performed for PJI. However, approximately half of all hospitals responded to the survey, which may have caused bias: it is uncertain whether the other hospitals would have given other answers. Nevertheless, it is improbable they would have given the straight and unanimous answers that would have changed the conclusions of this study. Also, the difference between the Netherlands and Belgium may, at least partly, be explained by the difference in responding hospitals: 44% versus 86% teaching hospitals.
Not many survey studies have been performed for PJI diagnosis and treatment. A survey on PJI treatment, sent to microbiologists, showed consensus on duration of postoperative antibiotic treatment (at least 4 weeks), but the antibiotic free period after that remained a point of discussion[45]. Anagnostakos and Kohn performed a study on diagnosis and treatment of hip PJI in 2011, and Holl *et al.* did the same on hip and knee PJI. Both written in German, their main conclusions were that the way to perform diagnosis and treatment differs between hospitals, and more guidance would be desirable[46,47].
Many factors in PJI diagnosis and treatment remain unclear, and many differences are seen between hospitals and between countries. Recently, guidelines have been published, but these are not (yet) followed accurately. On other questions, such as empirical antibiotic use, local antibiotics, use of spacers and the period before reimplantation should be considered, the guidelines do not give answers.

The variety between respondents indicates that more guidance is needed. Perhaps, nationally or locally adapted guidelines might be followed more directly. Standardized diagnosis and treatment options could result in an easier way to compare the outcome of different hospitals and diagnosis and treatment methods. This may result in better understanding how to treat patients with PJI and may decrease health care costs when a clear, evidence-based treatment protocol is used by all hospitals. Further research is definitely needed to answer most questions.

DIAGNOSIS
OF PERIPROSTHETIC JOINT INFECTIONS

CHAPTER 3

Does the Alpha Defensin ELISA test perform better than the Alpha Defensin lateral flow test for PJI diagnosis? A systematic review and meta-analysis of prospective studies

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CHAPTER 3

Does the Alpha Defensin ELISA test perform better than the Alpha Defensin lateral flow test for PJI diagnosis? A systematic review and meta-analysis of prospective studies

Abstract

Periprosthetic joint infection (PJI) following total joint arthroplasty is a serious complication that causes severe morbidity and adds a major financial burden to the healthcare system. Although there is plenty of research on the alpha-defensin (AD) test, a meta-analysis consisting of only prospective studies investigating AD's diagnostic efficacy has not been performed. Additionally, some important subgroups such as THA and TKA have not been separately analyzed, particularly regarding two commonly used versions of the AD test, the laboratory-based (ELISA) and lateral flow (LF).

Study questions were: (1) Does the AD ELISA test perform better in the detection of PJI than the AD LF test, in terms of pooled sensitivity and specificity, when including prospective studies only? (2) Are there differences in sensitivity or specificity when using AD ELISA and AD LF tests for PJI diagnosis of THA or TKA PJI separately?

Following the Preferred Reporting Items for Systematic reviews and Meta-Analyses guidelines, we included prospective studies describing the use of either AD test in the workup of pain after total joint arthroplasty (primary or revision, but not after resection arthroplasty). Fifteen studies (AD ELISA: 4; AD LF: 11) were included, with 1592 procedures. Subgroup data on THA and TKA could be retrieved for 1163 procedures (ELISA THA: 123; LF THA: 257; ELISA TKA: 228; LF TKA: 555). Studies not describing THA or TKA, those not using Musculoskeletal Infection Society (MSIS) criteria as the standard for determining the presence or absence of PJI, those not clearly reporting data for the AD test for the total cohort, and those describing data published in another study were excluded. Studies were not excluded based on follow-up duration; the MSIS criteria could be used within a few weeks, when test results were available. Quality was assessed using the Quality Assessment of Diagnostic Accuracy Studies-2 criteria. Study quality was generally good. The most frequent sources of bias were related to patient selection (such as unclear inclusion and exclusion criteria) and flow and timing (uncertainty in place and time of aspiration, for example). Heterogeneity was moderate to high; a bivariate random effects model therefore was used. To answer both research questions, sensitivity and specificity were calculated for AD ELISA and LF test groups and THA and TKA subgroups, and were compared using z-test statistics and meta-regression analysis.

No differences were found between the AD ELISA and the AD LF for PJI diagnosis in the pooled cohorts (THA and TKA combined), in terms of sensitivity (90% versus 86%; p = 0.43) and specificity (97% versus 96%; p = 0.39). Differences in sensitivity for PJI diagnosis were found between the THA and TKA groups for the AD ELISA test (70% versus 94%; p = 0.008); pooled AD LF test sensitivity did not differ between THA and TKA (80% versus 87%; p = 0.20). No differences in specificity were found in either subgroup.

Both the AD ELISA and AD LF test can be used in clinical practice because both have high sensitivity and very high specificity for PJI diagnosis. The lower sensitivity found for

diagnosis of PJI in THA for the AD ELISA test must be carefully interpreted because the pooled data were heterogenous and only two studies for this group were included. Future research should analyze TKAs and THAs separately to confirm or disprove this finding.

Introduction

Periprosthetic joint infection (PJI) is a devastating complication of total joint arthroplasty, that often leads to additional surgical procedures and prolonged intravenous antibiotic administration[8,48]. Because of its importance, and because of the difficulty of diagnosing it, many novel diagnostic biomarkers for PJI have recently been developed[49]. One of the best-described biomarkers in the past 5 years has been alpha-defensin (AD). AD is produced by neutrophils in synovial fluid. Higher levels indicate local infection[50]. AD levels can be measured in a laboratory with an ELISA (enzyme-linked immunosorbent assay) test developed by CD Diagnostics (Claymont, DE, USA). As a fast alternative, a point-of-care test using a lateral flow (LF) device (Synovasure®, Zimmer-Biomet, Warsaw, IN, USA) was developed. This LF test gives a result within 10 minutes.

According to the many meta-analyses performed in the last years, the ELISA test performs extremely well (sensitivity 95% to 100%, specificity 95% to 97%)[49,51–59], whereas the LF test appears not to be as good (sensitivity 71% to 85%, specificity 89% to 96%)[49,51,53,57–59]. However, most of these meta-analyses included multiple studies that seemed to count the same patients more than once, studies that used different criteria to diagnose PJI, and retrospective studies, which are more prone to bias. Furthermore, several relevant new studies have been published[60–64], and so a repeat meta-analysis is necessary. Also, most included studies mention both THA and TKA procedures, but possible differences in diagnostic accuracy in the tests between TKA and THA have not been separately analyzed.

We therefore performed a meta-analysis of all prospective studies comparing the AD ELISA test with the AD LF test for PJI in THA and TKA, and in it we sought to determine: (1) Does the AD ELISA test perform better in the detection of PJI than the AD LF test, in terms of pooled sensitivity and specificity, when including prospective studies only? (2) Are there differences in sensitivity or specificity when using AD ELISA and AD LF tests for diagnosis of THA or TKA PJI separately?

Methods

Search strategy and criteria

We designed a search to include all cohort studies on the diagnostic accuracy of the AD test (either ELISA or LF) in patients with PJI. A PubMed and EMBASE search was performed in August 2019, with the terms *Synovasure OR defensin AND infect* OR PJI*

AND prosth OR periprosth* OR arthroplast**, according to the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) statement[65]. Titles and abstracts were screened, full-text articles were assessed, data were extracted by two authors (JWPK, SJV), and conflicts were resolved by consensus. If needed, we contacted the study authors to provide details on their data.

Inclusion and exclusion criteria

All studies describing patient groups in which AD (either ELISA or LF) was used to evaluate pain after total joint arthroplasty were assessed (primary and revision but not resection arthroplasty). The exclusion criteria were symposium abstracts, studies solely describing joints other than the hip or knee, retrospective studies, studies using diagnostic criteria other than the original or modified Musculoskeletal Infection Society (MSIS) criteria as the gold standard for the presence or absence of PJI, and studies that did not provide data on the total cohort (that is, we could not retrieve correct data on the number of true positives, false positives, true negatives, and false negatives). If studies described possibly overlapping cohorts, the study with the larger cohort was included; of the 11 previous meta-analyses, 10 included studies with cohorts we believe may have the same patients. If AD was only used in a subgroup or as a second step in a classification tree, we excluded the study because of evident selection bias.

Data extraction

Two reviewers (JWPK, SJV) independently extracted relevant data including demographic, joint, and index test characteristics. Important variables such as antibiotics, comorbidities such as inflammatory conditions and the presence of metallosis, methods for obtaining synovial fluid samples, microbiological results, and data regarding diagnostic performance indexes (that is, sensitivity and specificity) were analyzed in detail to form subgroups, if possible. Cutoff or range definitions of the test, and whether these were predetermined by the study authors or derived with the use of receiver operating characteristic curves, were also noted.

Search results

The search identified 180 unique studies (Figure 1). After screening, 36 studies were selected for full-text review. No other studies were extracted from the reference lists of these studies. Of these 36, 21 were excluded: 13 retrospective studies[66–78], two studies solely on total shoulder arthroplasty[79,80], one study using other diagnostic criteria[81], two studies with a different cohort selection (one only included revision for aseptic loosening, excluding clear diagnoses of PJI[82], one study describing data on AD for only low-grade PJI with synovial C-reactive protein levels higher than 2 mg/L[83]), and three studies describing a cohort in another, larger study[84–86].

Fifteen studies were included in the final analysis, with a total of 1592 procedures (Table 1): four studies described the use of AD ELISA (Table 2)[50,62,87,88], and 11 of AD LF (Table 3)[21,60,61,63,64,89–94]. Subgroup data on THA and TKA could be retrieved for 1163

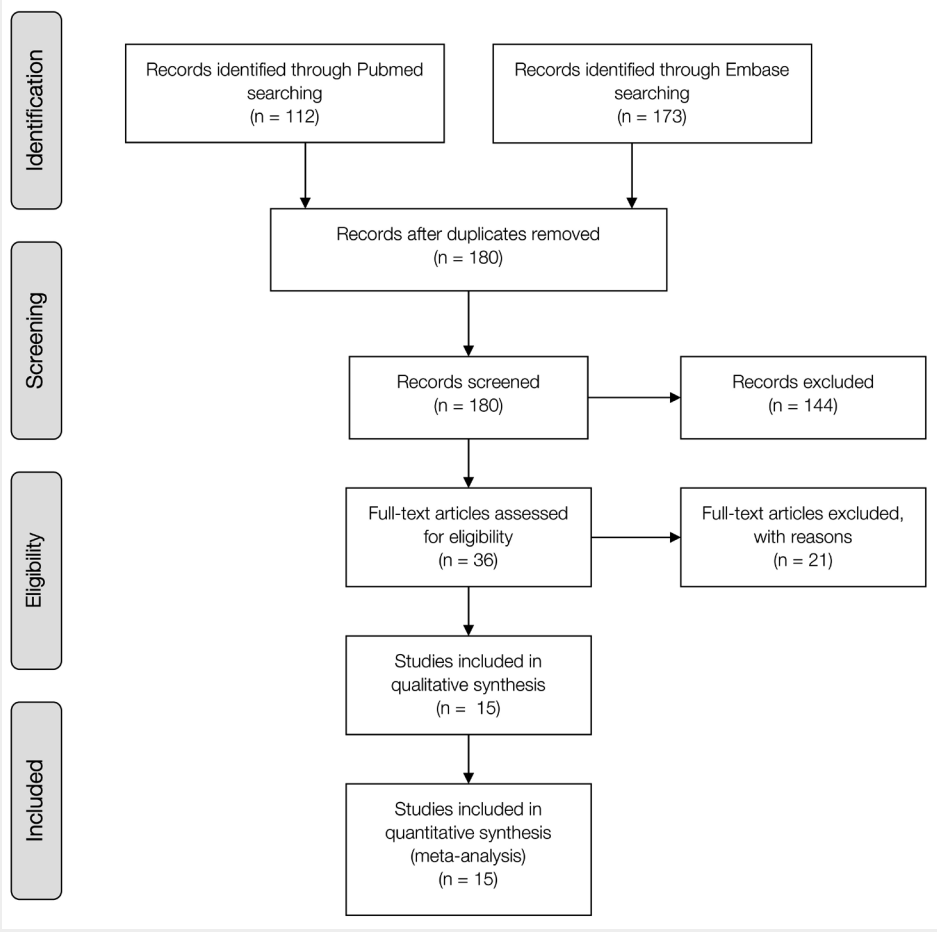


Figure 1: Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) flowchart showing the studies that were included in this meta-analysis[95].

procedures (ELISA THA: 123; LF THA: 257; ELISA TKA: 228; LF TKA: 555). There was no disagreement between the reviewers regarding the definitive inclusion of the studies.

Quality assessment

To assess the quality of the included studies, we used Quality Assessment of Diagnostic Accuracy Studies-2 (QUADAS-2) criteria[96]. This methodologic evaluation was independently performed by two authors (JWPK, SJV). Studies were not excluded from the systematic review based on methodologic quality. Quality of the included studies was generally good (Figure 2). Possible bias in patient selection (for example, unclear inclusions and exclusions) and flow and timing was seen in some studies, such as differences regarding aspiration location (outpatient clinic, operating room or radiology

Author	Year	Country	Joints	Antibiotics	Test	N	PJI (N)	% PJI	TP	FP	FN	TN	Aspiration at	PJI criteria	Blinding	Metallosis	Sinus tract
Deirmengian *et al.*[50]	2014	USA	THA/TKA	10	ELISA	149	37	24.8	36	5	1	107	OR/OP	MSIS	None	17/112, 3/5 FP	5/37
Frangiamore *et al.*[87]	2016	USA	THA/TKA	[a]	ELISA	78	24	30.8	24	1	0	53	OR	MSIS	None	excluded	4/24 (4 TP, 0 FN)
Kasparek *et al.*[89]	2016	USA/Austria	THA/TKA	[a]	LF	40	12	30.0	8	2	4	26	OR	Modified MSIS	None	excluded	
Berger *et al.*[91]	2017	Belgium	THA/TKA	[a]	LF	121	34	28.1	33	3	1	84	OR/OP	MSIS	None	1/3 FP	
Bonanzinga *et al.*[88]	2017	Germany	THA/TKA	≥ 2	ELISA	156	29	18.6	28	4	1	123	OR	Modified MSIS	MB, PA	2/4 FP	7/29 (6 TP, 1 FN)
Suda *et al.*[90]	2017	Germany	THA/TKA	PO	LF	30	13	43.3	10	3	3	14	OR	Modified MSIS	None	[a]	
Balato *et al.*[92]	2018	Italy	TKA	0	LF	51	16	31.4	14	1	2	34	OR	Modified MSIS	None	0	4/16
de Saint Vincent *et al.*[94]	2018	France	THA/TKA/TFA[b]	1	LF	39	8	20.5	7	4	1	27	OR	MSIS	None	1/4 FP	
Gehrke *et al.*[93]	2018	Germany	THA/TKA	Excluded	LF	195	76	39.0	70	0	6	119	DR	MSIS	None	excluded	3/76 (0 TP, 3 FN)
Plate *et al.*[63]	2018	Switzerland	TKA/THA	Excluded	LF	109	20	18.3	18	7	2	82	RD	Modified MSIS	MB, OS	1 TN	1/20 (0 TP, 1 FN)
Renz *et al.*[21]	2018	Germany	THA/TKA	PO	LF	212	45	21.2	38	6	7	161	[a]	Modified MSIS	None	[a]	12/45 (7 TP, 5 FN)
Riccio *et al.*[61]	2018	Italy	THA/TKA/TSA[b]	9	LF	71	38	53.5	32	1	6	32	DR	MSIS	None	0	
Tahta *et al.*[60]	2018	Turkey	TKA	Excluded	LF	38	17	44.7	16	0	1	21	OR	MSIS	None	0	
Sigmund *et al.*[64]	2019	Austria	THA/TKA	≥ 2	LF	101	29	28.7	20	4	9	68	OR	Modified MSIS	PA	[a]	1/29 (1 TP, 0 FN)
Kleiss *et al.*[62]	2019	Germany	THA/TKA	[a]	ELISA	202	55	27.2	43	5	12	142	[a]	Modified MSIS	None	5 (all TN)	14/55 (9 TP, 5 FN)

Table 1: Characteristics of the included studies; [a]Not mentioned.; [b]Procedures other than total hip arthroplasty (THA) and total knee arthroplasty (TKA) excluded;

PJI: periprosthetic joint infection; TP: true positive; FP: false positive; FN: false negative; TN: true negative; ELISA: enzyme-linked immunosorbent assay; LF: lateral flow; OR: operating room; OP: outpatient clinic; DR: dedicated room; RD: radiology department; MB: microbiologist; PA: pathologist; LS: laboratory staff; OS: orthopedic surgeon. TFA: total femur arthroplasty; TSA: total shoulder arthroplasty; PO: perioperative; MSIS: Musculoskeletal Infection Society.

Study	Year	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Deirmengian *et al.*[50]	2014	36	5	1	107	97% (86 to 100)	96% (90 to 99)
Frangiamore *et al.*[87]	2016	24	1	0	53	100% (86 to 100)	98% (95 to 100)
Bonanzinga *et al.*[88]	2017	28	4	1	123	97% (82 to 100)	97% (92 to 99)
Kleiss *et al.*[62]	2019	43	5	12	142	78% (65 to 088)	97% (92 to 99)
Combined		**131**	**15**	**14**	**425**	**90% (84 to 095)**	**97% (94 to 98)**

Table 2: Characteristics of the studies on the ELISA-based AD test; TP: true positive; FP: false positive; FN: false negative; TN: true negative; CI: confidence intervals; ELISA: enzyme-linked immunosorbent assay.

Study	Year	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Kasparek *et al.*[89]	2016	8	2	4	26	67% (35 to 90)	93% (76 to 99)
Suda *et al.*[90]	2016	10	3	3	14	77% (46 to 95)	82% (57 to 96)
Berger *et al.*[91]	2017	33	3	1	84	97% (85 to 100)	97% (90 to 99)
Balato *et al.*[92]	2018	14	1	2	34	88% (62 to 98)	97% (85 to 100)
Gehrke *et al.*[93]	2018	70	0	6	119	92% (84 to 97)	100% (97 to 100)
Renz *et al.*[21]	2018	38	6	7	161	84% (71 to 94)	96% (92 to 99)
de Saint Vincent *et al.*[94]	2018	7	4	1	27	88% (47 to 100)	87% (70 to 96)
Riccio *et al.*[61]	2018	32	1	6	32	85% (70 to 94)	97% (84 to 100)
Tahta *et al.*[60]	2018	16	0	1	21	94% (71 to 100)	100% (84 to 100)
Plate *et al.*[63]	2018	18	7	2	82	90% (68 to 99)	92% (84 to 97)
Sigmund *et al.*[64]	2019	20	4	9	68	69% (49 to 85)	94% (86 to 98)
Combined		**266**	**31**	**42**	**668**	**86% (82 to 90)**	**96% (94 to 97)**

Table 3: Characteristics of studies on the lateral flow AD test; ; TP: true positive; FP: false positive; FN: false negative; TN: true negative; CI: confidence intervals.

department) and the period between aspiration and revision (aspiration directly before revision surgery, or during diagnostic work-up). The possible use of lavage to obtain material was mentioned as an exclusion criterion only once specifically[21], but an insufficient amount of fluid was an exclusion criterion in almost all studies.

Statistical methods

To answer the two research questions, we calculated summary statistics for each study: sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV). To assess which model should be used for further analysis, between-study heterogeneity was assessed using the I^2 statistic. An I^2 value lower than 40% was considered low heterogeneity and a value of 0% meant that all variability in the effect size estimate was the result of sampling error within studies. We considered the following possible sources of heterogeneity a priori, and defined possible subgroups accordingly: affected joint (THA versus TKA), time from the index operation, use of antibiotics, and concomitant inflammatory diseases. Only the affected joint could be investigated; data on other possible sources of heterogeneity were insufficient. As heterogeneity was moderate to high, sensitivity, specificity, and respective 95% confidence intervals

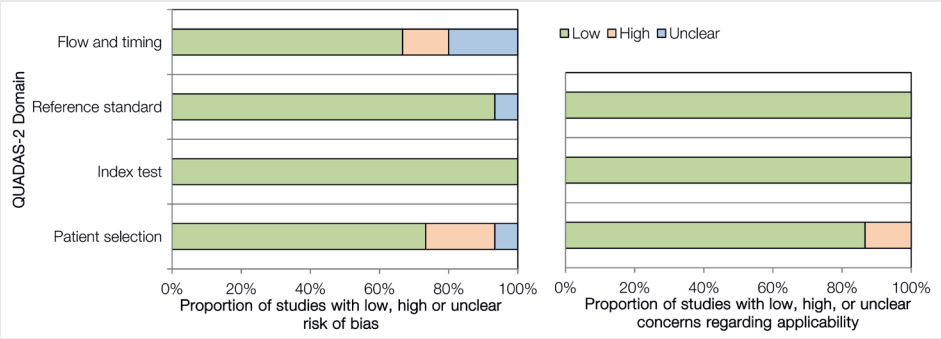


Figure 2: Quality Assessment of Diagnostic Accuracy Studies-2 (QUADAS-2) scores for (A) risk of bias and (B) concerns regarding applicability of the included studies, in percentages.

Study	Year	Test	TP	FP	FN	TN
Deirmengian *et al.*[50]	2014	ELISA	2	3	0	28
Kleiss *et al.*[62]	2019	ELISA	19	2	9	60
Combined			**21**	**5**	**9**	**88**
Kasparek *et al.*[89]	2016	LF	4	0	1	6
Suda *et al.*[90]	2016	LF	4	2	0	5
Berger *et al.*[91]	2017	LF	12	1	1	22
Renz *et al.*[21]	2018	LF	15	2	4	40
de Saint Vincent *et al.*[94]	2018	LF	4	1	0	9
Riccio *et al.*[61]	2018	LF	14	1	5	2
Plate *et al.*[63]	2018	LF	14	3	2	30
Sigmund *et al.*[64]	2019	LF	11	3	6	33
Combined			**78**	**13**	**19**	**147**

Table 4: Characteristics of included studies with data on total hip arthroplasties; TP: true positive; FP: false positive; FN: false negative; TN: true negative; ELISA: enzyme-linked immunosorbent assay; LF: lateral flow.

Study	Year	Test	TP	FP	FN	TN
Deirmengian *et al.*[50]	2014	ELISA	34	2	1	79
Kleiss *et al.*[62]	2019	ELISA	24	3	3	82
Combined			**58**	**5**	**4**	**161**
Kasparek *et al.*[89]	2016	LF	4	2	3	20
Suda *et al.*[90]	2016	LF	6	1	3	9
Berger *et al.*[91]	2017	LF	21	2	0	62
Balato *et al.*[92]	2018	LF	14	1	2	34
Renz *et al.*[21]	2018	LF	23	4	3	121
de Saint Vincent *et al.*[94]	2018	LF	3	3	1	18
Riccio *et al.*[61]	2018	LF	18	0	1	30
Tahta *et al.*[60]	2018	LF	16	0	1	21
Plate *et al.*[63]	2018	LF	4	4	0	52
Sigmund *et al.*[64]	2019	LF	9	1	3	35
Combined			**118**	**18**	**17**	**402**

Table 5: Characteristics of included studies with data on total knee arthroplasties (TKA); TP: true positive; FP: false positive; FN: false negative; TN: true negative; ELISA: enzyme-linked immunosorbent assay; LF: lateral flow.

Pooled group	Pooled group	Sensitivity (95% CI)	Sensitivity (95% CI)	Comparison	Specificity (95% CI)	Specificity (95% CI)	Comparison
Test 1	Test 2	Test 1	Test 2	p value	Test 1	Test 2	p value
LF: combined	ELISA: combined	86% (82-90)	90% (84-95)	0.43	96% (94-97)	97% (94-98)	0.39
LF: THA	LF: TKA	80% (71-88)	87% (81-93)	0.20	92% (86-96)	96% (93-97)	0.076
ELISA: THA	ELISA: TKA	70% (51-85)	94% (84-98)	0.008*	95% (88-98)	97% (93-99)	0.45
LF: THA	ELISA: THA	80% (71-88)	70% (51-85)	0.30	92% (86-96)	95% (88-98)	0.40
LF: TKA	ELISA: TKA	87% (81-93)	94% (84-98)	0.18	96% (93-97)	97% (93-99)	0.60

Table 6: Comparison of results for ELISA versus LF tests and THA versus TKA, combined and separately; ELISA: enzyme-linked immunosorbent assay; LF: lateral flow; THA: total hip arthroplasty; TKA: total knee arthroplasty; CI: confidence intervals; *significant result.

(CI) were calculated using the bivariate random-effects model suggested by DerSimonian and Laird[97].

For the first question, data were pooled for the ELISA and LF groups and sensitivity and specificity were calculated (Table 2 and 3). For the second research question, the same calculations were performed on the ELISA and LF data for THA and TKA separately (Table 4 and 5). For both questions, as the main study endpoint, sensitivity and specificity were pooled independently and were weighted by the inverse of the variance with the use of MetaDiSc 1.4 (Hospital Universitario Ramón y Cajal, Madrid, Spain)[98]. The logit-transformed sensitivity, specificity, and corresponding 95% CI of the index tests were compared using z-test statistics. A p value of < 0.05 was considered significant. We performed a meta-regression analysis using STATA 13.0 (StataCorp, College Station, TX, USA).

We could not investigate publication bias because tests addressing this type of bias require at least 10 studies and lower heterogeneity to be valid[99]. We calculated Spearman's correlation coefficient to assess a possible threshold effect, since difference studies might use different thresholds, such as a different cutoff value for a positive result of the ELISA-based test, which greatly influenced the estimation of summary points (sensitivity and specificity). The threshold for the ELISA-based reference test was mentioned in all four studies (5.2 mg/L[87] or signal-to-cutoff ratio 1.0[50,62,88]). No threshold effect (suggested by a strong positive correlation) was found (Spearman's correlation coefficient: -0.400; p = 0.600)[100].

Results

AD ELISA versus AD LF test (THA and TKA data combined)

After pooling data from studies on PJI in THA and TKA combined, we found no differences in sensitivity between the AD ELISA and LF tests: 90% (95% CI 84 to 95) versus 86% (95% CI 82 to 90) (p = 0.43) (Figure 3). Likewise, we identified no differences in specificity between the two tests: 97% (95% CI 94 to 98) versus 96% (95% CI 94 to 97) (p = 0.39) (Table 6). We found that PPV was 90% for the AD ELISA and 90% for the AD LF test; NPV was 97% for the AD ELISA test and 94% for the AD LF test.

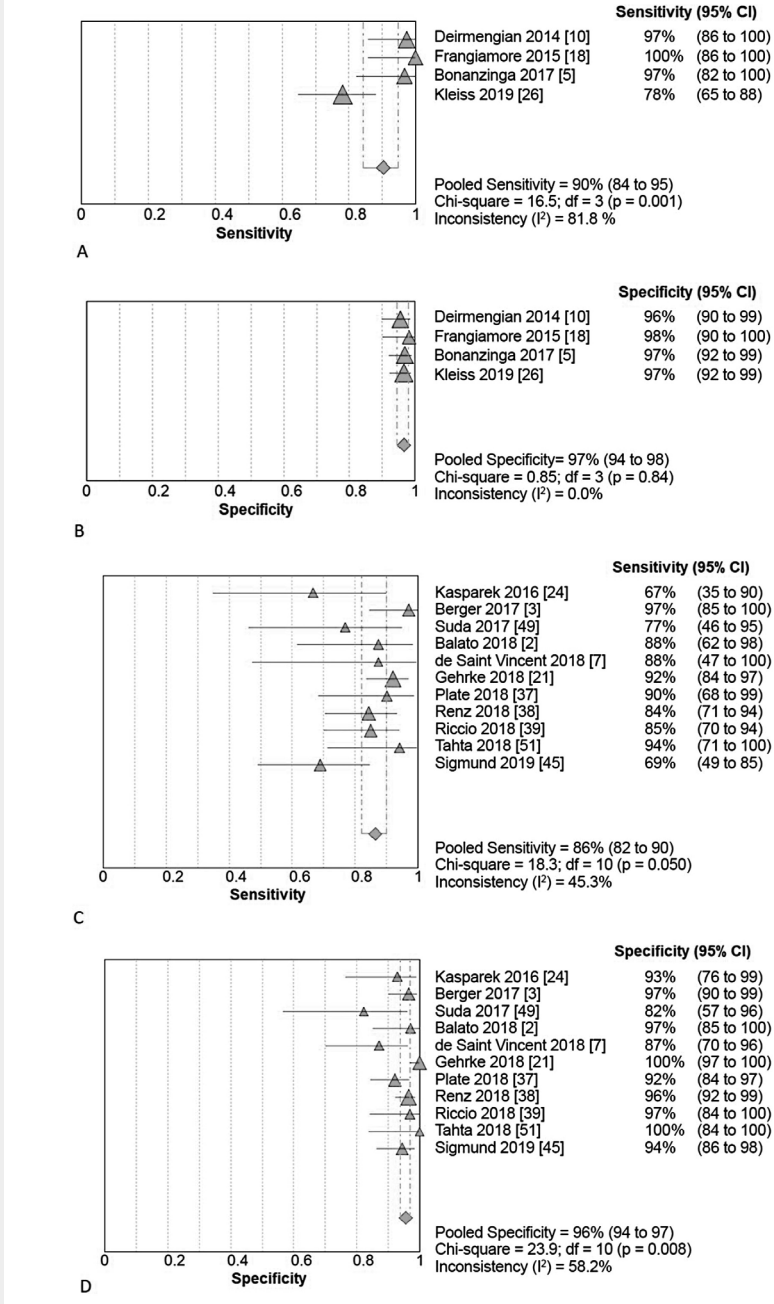


Figure 3: Forest plots showing (A) sensitivity and (B) specificity for the ELISA-based alpha-defensin test and (C) sensitivity and (D) specificity for the alpha-defensin lateral flow test; ELISA: enzyme-linked immunosorbent assay; CI: confidence intervals; df: data frame.

AD ELISA versus AD LF test when assessing THA and TKA data separately

We found no differences between the AD ELISA test and AD LF test in terms of sensitivity for PJI diagnosis in THA: 70% (95% CI 51 to 85) versus 80% (95% CI 71 to 88) (p = 0.30). Likewise, for specificity, we found no differences: 95% (95% CI 88 to 98) versus 92% (95% CI 86 to 96) (p = 0.40) (Table 6). For THA, PPV was 81% for ELISA, and 86% for LF; NPV was 91% for ELISA and 89% for the AD LF test.

For PJI diagnosis in TKA, AD ELISA and LF tests showed no differences in sensitivity: 94% (95% CI 84 to 98) versus 87% (95% CI 81 to 93) (p = 0.18). For specificity, we identified no differences: 97% (95% CI 93 to 99) versus 96% (95% CI 93 to 97) (p = 0.60). The PPV for TKA subgroups was 92% for ELISA and 87% for the AD LF test, and NPV was 98% for ELISA, and 96% for LF.

When comparing THA and TKA, we found the AD ELISA test was more sensitive in diagnosing PJI in TKA than in THA: 94% (95% CI 84 to 98) for TKA versus 70% (95% CI 51 to 85) for THA (p = 0.008). Specificity of the AD ELISA test was not different between THA and TKA: 95% (95% CI 88 to 98) versus 97% (95% CI 93 to 99) (p = 0.45).

For the AD LF test, we saw no differences in sensitivity between THA and TKA: 80% (95% CI 71 to 88) versus 87% (95% CI 81 to 93) (p = 0.20). Specificity also showed no differences: 92% (95% CI 86 to 96) versus 96% (95% CI 93 to 97) (p = 0.076).

Discussion

Background

PJI is a substantial problem in orthopedic practice, and consequently, new diagnostic biomarkers are constantly being developed[49]. AD has been described in many clinical studies and meta-analyses, but they all have shortcomings: some included multiple studies with (partly) the same cohorts; others included studies using different criteria to diagnose PJI, risking increased heterogeneity; in addition, all meta-analyses included retrospective studies, which are often of lower quality and more at risk for confounding and bias[49,51–59]. In this meta-analysis, we found no differences between the AD ELISA test and AD lateral flow test in terms of sensitivity and specificity. In subgroup analysis, the ELISA test demonstrated higher sensitivity for diagnosing PJI in TKA compared with THA. However, some nuance on this result is essential: the pooled group is small (only two included studies), and heterogenous. Also, differences in diagnostic workup between TKA and THA are likely, but data were insufficient to study this.

Limitations

Although only prospective studies were included and strict inclusion and exclusion criteria were applied, the heterogeneity of the included studies is one of the major shortcomings of this meta-analysis. Small differences in patient cohorts of the included studies, such as differences in aspiration location, aspiration techniques, possible use of lavage, and the period between aspiration and revision, probably are the main reason for this heterogeneity. For example, differences in aspiration technique between THA (operating

room or radiology department) and TKA (usually done in the outpatient clinic) are very likely. Unfortunately, as full specifics were not given, pooling heterogeneous data was unavoidable. It is therefore possible that the absence of differences between the ELISA and LF test found in this study only applies for this selection of (heterogenous) studies. Although this is a substantial limitation, differences between hospitals in daily practice are also considerable, rendering the described results applicable to orthopedic practice in general, with careful interpretation.
We also raise a concern about publication bias of studies on this subject: more than half of the included studies reported conflicts of interest concerning the AD test. We hope there will be more studies in the future from authors not directly connected to manufacturers of the tests being studied.
Furthermore, the lower sensitivity for THA PJI diagnosis for AD ELISA-based test alone is largely based on the results of a single study[62]. Separate data on THA and TKA could only be retrieved for two studies describing the AD ELISA test[50,62], resulting in a fairly small pooled group (Table 4 and 5). Several differences between these studies exist, such as the use of biopsy to obtain cultures in cases of borderline PJI criteria fulfillment (21%) in one study[62], which was not described in the other study[50]. Hematoma formation after biopsy, and subsequent dilution, for example, may be a reason for false negative results, but this has never been described in any study. Because only two studies could be included, the greater sensitivity of the AD ELISA test in TKA compared with THA should be interpreted with great caution.

AD ELISA versus AD LF test (THA and TKA data combined)
In terms of sensitivity and specificity, we found no differences between the AD ELISA and LF test, when we pooled THA and TKA data. Both tests showed high sensitivity and very high specificity for PJI diagnosis. These test characteristics make either test a useful addition to the array of diagnostic tools currently available for PJI; the ELISA-based test results take a day but allow a more nuanced interpretation with continuous values, and the lateral flow test provides a yes/no result within 10 minutes. However, one must keep the above-mentioned limitations in mind when interpreting AD tests for individual patients. When comparing these results with previous studies, the sensitivity of the ELISA test is slightly lower than previously described, and the LF test performed slightly better in terms of sensitivity and specificity than reported in most earlier studies (Table 7). The publication of new studies included in this meta-analysis is probably the most important explanation for these differences.

AD ELISA versus AD LF test when assessing THA and TKA data separately
When pooling data for THA and TKA separately, we found a lower sensitivity of the AD ELISA test alone for THA PJI diagnosis, compared with TKA. We found no other differences. For clinical practice, when interpreting the results of the AD ELISA test for THA PJI, one should keep in mind that sensitivity may be lower than for TKA. Recognizing the caveats mentioned in the limitations section, these findings may also partly be explained by differences between THA and TKA PJI. Hypothetically, the type of joint should not

Author	Year	Included studies (n)	Included studies	Sensitivity ELISA	Specificity ELISA	Sensitivity LF	Specificity LF
Wyatt *et al.*[55]	2016	6	50,66,67,79,85,86	100%	96%		
Li *et al.*[54]	2017	4	50,66,85,87	98%	97%		
Xie *et al.*[56]	2017	6	50,66,67,79,86,87	96%	95%		
Lee *et al.*[52]	2017	7	50,66–68,85–88	97%	96%		
Yuan *et al.*[53]	2017	11	50,66,90,67,79,84–89	97%	96%	80%	89%
Eriksson *et al.*[58]	2018	7	50,66,84,87–90	96%	96%	71%	90%
Suen *et al.*[57]	2018	10	50,66,79,84–90	95%	97%	77%	91%
Ahmad *et al.*[49]	2018	10	50,66,79,84–90	97%	97%	80%	89%
Marson *et al.*[51]	2018	11	50,66,93,84,85,87–92	95%	97%	85%	90%
Carli *et al.*[59]	2019	16	21,50,90–94,102,66,74,84–89	97%	97%	82%	96%
Current study	2020	15	21,50,90–94,60–64,87–89	90%	97%	86%	96%

Table 7: Meta-analyses describing pooled results for ELISA-based and (in some studies) both ELISA and LF alpha-defensin tests. One meta-analysis did not mention sensitivity and specificity[103]; ELISA: enzyme-linked immunosorbent assay; LF: lateral flow.

influence the results of the AD test (ELISA-based or LF) because these patients all have the same immune response. However, differences in joints exist. First, they have different volumes, thus possibly influencing the AD concentration. Furthermore, PJI in different joints has different causative organisms, at least for shoulder versus hip and knee PJI[101]. AD is known to be less sensitive in diagnosing PJI of the shoulder: two studies on the ELISA-based AD test for PJI in shoulder arthroplasty found comparable high specificities (95% to 96%) but lower sensitivities (63% to 75%)[79,80]. In light of our findings, we would recommend authors describe test results for THA and TKA separately in addition to overall results, which should help confirm or disprove the difference in sensitivity that was found.

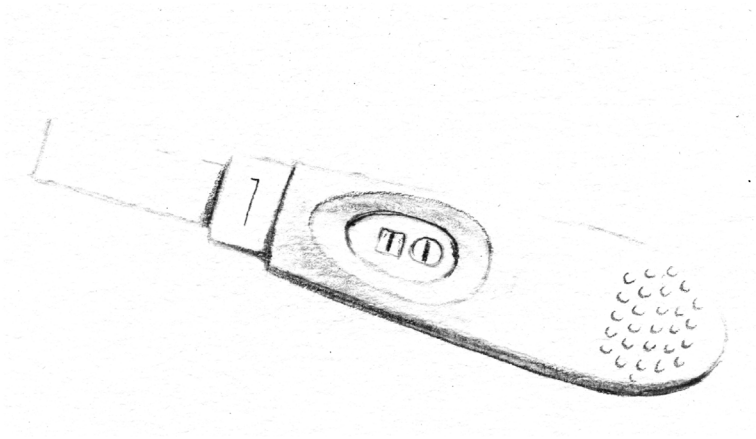
Conclusions

We found no differences in sensitivity or specificity between the ELISA and LF AD test after pooling all included studies, and we did not find that the AD ELISA test was superior. For THA and TKA subgroups, sensitivity was found to be lower for THA PJI diagnosis than for TKA PJI diagnosis when using the AD ELISA test as well as for the ELISA and LF AD test combined. For clinical practice, this study confirms that both tests have good sensitivity and specificity, and implementation in diagnostic routines is justifiable. This study provides no arguments to favor the AD ELISA test over the AD LF test. However, with the heterogeneity of the pooled groups, and the availability of only two studies with separate THA and TKA data for the AD ELISA test, these results must be considered carefully. Further studies are indispensable for a more thorough assessment of differences between THA and TKA, and analysis of different subgroups may provide information about patients in whom the AD test will be most useful. We encourage researchers to specify which joint(s) is/are being studied, the criteria used to determine PJI (including the presence or absence of a sinus tract), timing of the possible infection (acute or chronic), pretreatment with antibiotics (if any), the presence or absence of metallosis, and the location and method of aspiration (including management of dry taps).

DIAGNOSIS
OF PERIPROSTHETIC JOINT INFECTIONS

CHAPTER 4

Good accuracy of the alpha-defensin lateral flow test for hip PJI: a pilot study in a retrospective cohort of 52 patients



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CHAPTER 4

Good accuracy of the alpha-defensin lateral flow test for hip PJI: a pilot study in a retrospective cohort of 52 patients

Abstract

The alpha-defensin lateral flow (AD LF) test is a new diagnostic tool for periprosthetic joint infection (PJI). Test accuracy for combined cohorts of hip and knee PJI has been reported to be good. The aim of this study was to assess the accuracy of the AD LF test for hip PJI, and to compare three different diagnostic criteria for PJI.
A cohort of 52 patients was identified, with a painful or poor-functioning total hip - or hemi-arthroplasty, that underwent aspiration and a subsequent AD LF test. PJI was diagnosed with MSIS (Musculoskeletal Infection Society) criteria, and sensitivity, specificity, overall accuracy, positive predictive value (PPV) and negative predictive value (NPV) were calculated. Furthermore, test specifics were compared with the EBJIS (European Bone and Joint Infection Society) and ICM 2018 (International Consensus Meeting) criteria for PJI.
Using MSIS criteria, sensitivity was 100% (CI 54% – 100%) and specificity was 89% (CI 76% – 96%). Six true positives and five false positives were found, including one case of metallosis. Using EBJIS criteria, more PJI were found (11 versus six), sensitivity was lower (71%, CI 42% – 92%) and specificity was higher (97%, CI 86% – 100%), with four false negatives and one false positive result. Using ICM 2018 criteria, sensitivity was 91% (62% – 100%) and specificity 100% (91 – 100%). The results in this cohort are comparable to previous studies.
Overall test accuracy of the AD LF test was good in this cohort, with a sensitivity of 100% and specificity of 89%. Using different PJI definition criteria, sensitivity and specificity changed slightly but overall accuracy remained around 90%. Using the AD LF test in metallosis cases can result in false positive results and should be performed with caution.

Introduction

Periprosthetic joint infection (PJI) is one of the most serious complications of total hip arthroplasty (THA). It generally requires one or more operations, weeks of hospitalization and long courses of antibiotic treatment. Overall, it is a considerable financial and logistic burden to hospitals and the health care system in general[8,104]. The patients themselves, however, are the ones most afflicted by this complication. Treatment methods range from curative therapy with revision arthroplasty to months of living without a functioning hip articulation (Girdlestone procedure) or to life-long suppressive antibiotic therapy (for inoperable patients with a low grade PJI)[8].
Because treatment of PJI differs from other revision indications, it is important to accurately exclude PJI before revision surgery takes place. PJI can be challenging to diag-

nose and several definitions have been proposed in the past. The most recent (modified) definition by the Musculoskeletal Infection Society (MSIS) includes various laboratory values and aspiration results[18]. This definition has been used as the gold standard for PJI in the last decade. However, in the last years, two new definitions have been suggested: the European Bone and Joint Infection Society (EBJIS) has recently proposed other diagnostic criteria which may have a lower threshold for the detection of PJI, and therefore possibly a higher specificity[21]; the 2018 International Consensus Meeting (ICM 2018) criteria includes the most recent tests into a cumulative score, with substantially higher sensitivity and specificity[19].
None of the criteria are ideal in terms of speed, ease of use, high sensitivity and high specificity. Therefore, new diagnostic tools are constantly being developed. One of the most studied new diagnostic markers of the last few years is the determination of alpha-defensin (AD), a protein released by white blood cells in synovial fluid. Two different versions to test this exist: the alpha-defensin immunoassay test, which is a laboratory test with a readout within 24 hours; and the Synovasure® lateral flow test (Synovasure®, Zimmer Biomet, Warsaw, Indiana). This point-of-care test can show directly whether an arthroplasty might be infected, but may have lower accuracy[58,90,94].
The aim of this pilot study was to identify a cohort of patients in whom the alpha-defensin lateral flow (AD LF) test was already performed in the last two years in our hospital, and to assess the accuracy of the AD LF test for this cohort (sensitivity, specificity, PPV, NPV) by comparing it to the current gold standard for the diagnosis of PJI. As a secondary aim, the more recently proposed EBJIS and ICM 2018 definitions were applied to the cohort as well, to investigate the differences between the definitions.

Methods

Since 2015, one of the orthopedic surgeons in our hospital, with a subspecialty in PJI, started using the AD LF test (Synovasure®, Zimmer Biomet, Warsaw, Indiana) for all aspirations of potential hip PJI. This cohort was identified by using our own database and cross-referencing with surgical records. Data were retrospectively collected and analyzed. Patients were included if an AD LF test was performed after aspiration of THA or hip hemi-arthroplasty (HHA) in the study period. Exclusion criteria were: significantly incomplete medical record data (e.g., missing culture results, unavailable data on surgery performed elsewhere), aspiration of other arthroplasty than THA or HHA, unavailability of AD LF test (not performed or missing data).

Intervention

All patients underwent sterile aspiration of the hip joint as part of the diagnostic work-up for a painful or poorly functioning hip arthroplasty, between January 2015 and March 2018. This aspiration was performed in the operating room under sterile conditions with the help of fluoroscopy. After aspiration, the AD LF test was performed according to manufacturer guidelines if enough material was available (e.g., no dry tap). A white blood

cell count (WBC) and polymorphonuclear neutrophil percentage (PMN%) were performed, and one or two samples were used for culturing in blood culture bottles (aerobic and anaerobic).

Revision surgery

During revision surgery, at least six tissue cultures were collected, from joint capsule/synovium, acetabular and femoral interface. Sonication and histopathology were not standardly performed during the study period. Antibiotic treatment was guided by prior cultures results, or vancomycin (1000 milligrams twice daily) was administered until culture results were known, which could take up to 14 days.

Data

After identification of all patients that underwent aspiration, the following data were collected: patient characteristics; arthroplasty details (time after initial surgery, hemi or total hip arthroplasty, articulation, use of cement); C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), serum leukocyte count and presence of a sinus tract at presentation; aspiration characteristics (amount, aspect, AD LF test results, WBC and PMN%, number of cultures and culture results); follow-up data (revision performed, intraoperative histology and culture results, diagnosis, PJI criteria met).

PJI definition

Three recent definitions of PJI for calculation of test accuracy were used. The MSIS definition was used as the standard [18]. EBJIS and ICM definitions were also used for comparison[19,21]prompted us to develop an evidence-based and validated updated version of the criteria. Methods: This multi-institutional study of patients undergoing revision total joint arthroplasty was conducted at 3 academic centers. For the development of the new diagnostic criteria, PJI and aseptic patient cohorts were stringently defined: PJI cases were defined using only major criteria from the MSIS definition (n = 684. See Table 1-3.

Study parameters

The main aim of this study was to assess sensitivity and specificity with PPV and NPV of the AD LF test, using the MSIS criteria for PJI as mentioned above. The second aim was to compare these criteria with the EBJIS and ICM 2018 criteria.

Statistical analysis

To assess the performance of the AD LF test, the sensitivity, specificity, PPV and NPV were calculated. Except for age, the scale variables were described using the median and the range regarding a non-normal distribution measured by means of the one-sample Kolmogorov-Smirnov test. 95% confidence intervals (CI) were calculated and are described.

- Two or more positive periprosthetic cultures with phenotypically identical organisms, or
- A sinus tract communicating with the joint, or
- Having at least three of the following minor criteria:
    - elevated serum C-reactive protein (CRP) >10mg/L AND erythrocyte sedimentation rate (ESR) > 30 mm/h;
    - elevated synovial fluid white blood cell (WBC) count 3.000 cells/µL OR ++ result on leukocyte esterase test strip;
    - elevated synovial fluid polymorphonuclear neutrophil percentage (PMN%) >80%;
    - positive histological analysis of periprosthetic tissue;
    - a single positive culture.

Table 1: Modified MSIS (Musculoskeletal Infection Society) criteria for periprosthetic joint infection definition[18].

- Sinus tract OR purulence around the prosthesis;
- Acute inflammation on histopathology of periprosthetic tissue;
- Elevated synovial fluid white blood cell (WBC) count of more than 2.000 cells/µL OR elevated synovial fluid polymorphonuclear neutrophil percentage (PMN%) >70%;
- Microbial growth in synovial fluid OR > 2 tissue samples (for highly virulent microorganisms already one positive sample confirms infection) OR sonication fluid (≥ 50 CFU/ml).

Table 2: EBJIS (European Bone and Joint Infection Society) criteria for periprosthetic joint infection (PJI) definition. One or more criteria fulfilled means positive PJI diagnosis[21]; CFU: colony forming units.

Major criteria (at least one of the following):	
Two positive cultures of the same organism Sinus tract with evidence of communication to the joint or visualization of the prosthesis	**Infected**

Preoperative score: minor criteria	**Score**	**Decision**
Serum: elevated CRP *or* D-Dimer	2	≥6: infected 2-5: possibly infected* 0-1: not infected
Serum: elevated ESR	1	
Synovial: elevated synovial WBC count *or* LE	3	
Synovial: positive alpha-defensin	3	
Synovial: elevated synovial PMN (%)	2	
Synovial: elevated synovial CRP	1	

Intraoperative score: minor criteria (Inconclusive preoperative score* *or* dry tap)	**Score**	**Decision**
Preoperative score	-	≥6: infected 4-5: inconclusive 0-3: not infected
Positive histology	3	
Positive purulence	3	
Single positive culture	2	

Table 3: ICM 2018 (International Consensus Meeting) scoring criteria for periprosthetic joint infection definition[19]; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; WBC: white blood cell count; PMN: polymorphonuclear neutrophils.

Figure 1: Flowchart of patient selection and periprosthetic joint infection (PJI) diagnosis according to MSIS (Musculoskeletal Infection Society), EBJIS (European Bone and Joint Infection Society) and ICM (International Consensus Meeting) 2018 criteria; AD: alpha-defensin.

Results

Demographics

Between January 2015 and December 2017, 83 hip aspirations were conducted. 31 patients were excluded because the AD LF test was not performed. Therefore, a total of 52 patients (52 aspirations) were included in this pilot study, with a mean age of 72 years. See Table 4 for demographics and comparison with the excluded patients. The median time between primary surgery and aspiration was 35 months (range 3-266 months) and 46 (88%) patients had a total hip arthroplasty (THA). 31 of 46 THA patients had a metal on polyethylene (MoP) articulation. The median CRP and ESR before aspiration were 6 mg/L (range 1-195 mg/L) and 13 mm/hour (range 3-120 mm/hour) respectively, and the median white blood cell count (WBC) in synovial fluid was 800 cells/µL (range 10 – 264.000 cells/µL).

	Cohort	Excluded
Total [n]	52	31
Age [mean (SD), years)	72 (9.2)	67.5 (9.5)
Gender [n]		
Male	24	12
Female	28	19
Operated side [n]		
Right	28	12
Left	24	19
Prosthesis [n]		
Total hip arthroplasty	46	26
Hip hemi-arthroplasty	6	5
Articulation [n]		
MoP	31	18
CoP	8	4
CoC	4	3
MoM	3	1
HHA	6	5
Time to aspiration [Median (range), months]	35 (3-266)	32.4 (3-191)

Table 4: Demographics of the described cohort and the group of excluded patients (no alpha-defensin lateral flow test performed); SD: standard deviation; MoP: metal on polyethylene; CoP: ceramic on polyethylene; CoC: ceramic on ceramic; MoM: metal on metal; HHA: hip hemi-arthroplasty.

AD LF test

In 11 patients (21%) the AD LF test was positive. According to the MSIS criteria, six patients had a PJI. Using these criteria, sensitivity was 100% (CI 54%-100%), specificity was 89% (CI 76% – 96%), PPV was 55% (CI 34% - 73%) and NPV was 100%. The overall accuracy was 90% (CI 79% - 97%). None of the AD LF test results were false negative and five were false positive (Figure 1). One of the false positive cases had a metal-on-metal (MoM) articulation. See Table 5 for details on all positive AD LF tests or inconclusive/positive criteria.

Revision surgery

In total, 19 patients underwent revision surgery after aspiration. Ten of these had no PJI suspicion and underwent direct revision. In eight patients, PJI was suspected because of aspiration results or symptoms, and a two-stage revision was performed. In one patient, debridement, antibiotics, irrigation and implant retention (DAIR) was performed because PJI was classified as acute hematogenous (symptom duration of 8 days with a prior well-functioning THA).

PJI

Of 6 patients with PJI, five patients (83%) underwent revision surgery. One patient was treated with suppressive antibiotics because of extensive co-morbidity, and died 5 months later, unrelated to PJI.

Case	*Criteria*	A	B	C	D	E	F	G	H	I	PJI?							
	Art	Sinus tract	Visible purulence	CRP (mg/L)	ESR (mm/hour)	WBC count (cells/µL)	PMN%	Culture synovial fluid (nr of cultures)	Culture tissue (nr of cultures)	AD	MSIS (+/- ; criteria)		EBJIS (+/- ; criteria)		ICM 2018 (+/-/i* ; criteria		Revision surgery	one- or two-stage
1	CoC	-	-	6,5	21,0	19100	91	neg (1)	neg (6)	+	-	E,F	+	E,F	+	E,F,I	Yes	two-stage
2	MoP	yes	-	9,0	23,0	-	-	pos (2)	pos (8/9)	+	+	A,G,H	+	A,G,H	+	A,G,H,I	Yes	two-stage
3	MoP	-	-	8,5	29,0	3000	4	neg (2)	-	-	-		+	E	-		No	-
4	MoP	-	-	9,8	16,0	6200	77	neg (2)	pos (5/8)	+	+	E,H	+	E,F,H	+	E,H,I	Yes	two-stage
5	CoC	-	-	6,9	10,0	2300	-	neg (1)	-	-	-		+	E	-		No	-
6	MoP	-	-	12,0	26,0	10	-	neg (2)	pos (1/2)	-	-	C,H	-		i*	C,H	Yes	one-stage
7	MoP	-	-	-	-	9350	-	neg (1)	-	-	-	E	+	E	-	E	No	-
8	HHA	-	-	-	-	-	-	neg (1)	pos (1/6)	+	-	H	-		i*	H,I	Yes	one-stage
9	MoP	-	-	144,0	64,0	37300	92	pos (1/2)	pos (2/6)	+	+	C,D,E,F,G,H	+	E,F,G,H	+	C,D,E,F,H,I	Yes	DAIR
10	MoP	-	-	61,0	72,0	7900	95	pos (1/1)	pos (9/9)	+	+	C,D,E,F,G,H	+	E,F,G,H	+	C,D,E,F,H,I	Yes	two-stage
11	MoP	-	-	71,0	55,0	35300	97	pos (2/2)	pos (7/7)	+	+	C,D,E,F,G,H	+	E,F,G,H	+	C,D,E,F,H,I	Yes	two-stage
12	HHA	-	-	9,6	-	4900	81	-	-	+	-	E,F	+	E,F	+	E,F,I	No	-
13	MoM	-	yes	195,0	-	264000	96	neg (2)	-	+	+	B,C,E,F	+	B,E,F	+	B,C,E,F,I	No	-
14	MoP	-	-	15,0	13,0	8000	-	neg (1)	neg (6)	+	-	C,E	+	E	+	C,E,I	Yes	two-stage
15	HHA	-	-	1,0	9,0	4000	15	neg (2)	-	-	-	E	+	E	-	E	No	-
16	MoM	-	-	5,7	8,0	5170	52	neg (3)	-	+	-	E	+	E	+	E,I	No	-

Table 5: Characteristics of all patients with positive alpha-defensin (AD) lateral flow test and/or positive or inconclusive criteria; Art: articulation; CoC: ceramic on ceramic; MoP: metal on polyethylene; MoM: metal on metal; HHA: hip hemi-arthroplasty; CoP: ceramic on polyethylene; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; WBC: white blood cells; PMN%: polymorphonuclear neutrophil percentage; neg: negative; pos: positive; PJI: periprosthetic joint infection; MSIS: Musculoskeletal Infection Society; EBJIS: European Bone and Joint Infection Society; ICM: international consensus meeting; i*: inconclusive; DAIR: debridement, antibiotics, irrigation and implant retention.

Case	Culture after aspiration (positive cultures/nr of total cultures)	Culture after revision (positive cultures/nr of total cultures)
2	*Cutibacterium acnes* (2/2) *Staphylococcus aureus* (1/2)	*Cutibacterium acnes* (8/9)
4	negative (2/2)	*Staphylococcus capitis* (5/8) *Staphylococcus hominis* (1/8) *Staphylococcus epidermidis* (1/8) *Cutibacterium acnes* (1/8)
7	negative (2/2)	*Cutibacterium acnes* (1/2)
8	negative (1/1)	*Staphylococcus capitis* (1/6)
9	*Staphylococcus aureus* (1/2)	*Staphylococcus aureus* (2/6)
10	*Pseudomonas aeruginosa* (1/1)	*Pseudomonas aeruginosa* (9/9) *Staphylococcus epidermidis* (1/9)
13	*Staphylococcus lugdunensis* (2/2)	*Staphylococcus lugdunensis* (7/7)

Table 6: All cases of positive cultures in the described cohort including case number.

Seven cases (of 19 revisions) had positive cultures (Table 6). In four of these seven patients, the microorganism found intraoperatively corresponded to aspiration culture results. The other three patients had negative preoperative synovial cultures. Two of these did not meet PJI criteria (both MSIS and EBJIS), as they had only one positive intraoperative culture with a low virulence microorganism (*Cutibacterium acnes* and *Staphylococcus capitis*). Both patients underwent direct revision, without macroscopic suspicion of PJI, and were free of symptoms at the last follow-up. One patient was treated with DAIR, as described above. The other four patients with positive cultures underwent two-stage revision.

Metal on metal

Three patients (6%) had a metal on metal (MoM) hip articulation. One patient was not suspected of PJI. The two other patients had a positive AD LF test (67%): one patient did not meet MSIS PJI criteria, but did have PJI according to EBJIS criteria (elevated WBC count of 5170 cells/μL). The last patient had PJI, according to both MSIS and EBJIS criteria. Due to severe comorbidity, this patient was considered inoperable, as a result of which intraoperative cultures were never obtained.

EBJIS criteria

When adhering to the criteria by the EBJIS, PJI was found in 14 patients and the AD LF test had a sensitivity of 71% (CI 42% – 92%), specificity of 97% (CI 86% – 100%), PPV of 91% (CI 58% – 99%) and NPV of 90% (CI 80% – 96%). The overall accuracy was 90% (CI 79% - 97%). Using the EBJIS criteria, four AD LF test results were false negative and one was false positive (Figure 1).

ICM 2018 criteria

10 patients had PJI according to these criteria, and 40 patients had no PJI. Two cases were inconclusive, one with positive and 1 with negative AD LF test. Excluding these cases, no false positives and false negatives were found, and the AD LF test had 100% sensitivity (69% – 100%) and specificity (91 – 100%). When classifying these cases as infected, as they are likely to be treated as infected cases, sensitivity was 91% (62% – 100%), specificity 100% (91 – 100%). PPV, NPV and accuracy were 100%, 98% (86% – 100%) and 98% (90% – 100%), respectively.

Discussion

In this study the accuracy of the AD LF test was assessed in 52 patients with a suspicion of hip PJI.

The measured sensitivity and specificity of the AD LF test were 100% and 89% respectively, with an overall accuracy of 90%. In comparison, when applying the EBJIS criteria, sensitivity and specificity were 71 and 97% respectively. Overall accuracy was the same, 90%. When using the new ICM 2018 criteria, a sensitivity of 91% and a specificity of 100% were found, with an accuracy of 98%.

The existing literature describes a large range in sensitivity and specificity. This can partly be explained by study-related factors. The results for sensitivity range from 67.0% to 97.1% and for specificity from 82.4% to 100%[21,84,90–92,94]. The results of the current study are comparable to these studies.

Renz *et al.* also reported results of the AD LF test when using EBJIS criteria, and found a sensitivity of 54.4%, specificity of 99.3%, PPV of 97.7%, and NPV of 78.6% (for MSIS criteria these numbers were 84.4%, 96.4%, 86.4% and 95.8%, respectively)[21]. In a cohort of 212 patients, 45 patients had PJI according to MSIS criteria, and 79 with the use of EBJIS criteria. With this lower threshold, the prevalence of PJI is higher and the number of false positives is lower. This is similar for the current study. The only study on the new ICM 2018 criteria[19] is the one in which the definition is proposed, and they described no accuracy of the AD test alone. Since the AD test is used in the criteria, one may argue that it is not a good gold standard to assess the accuracy of the AD test itself.

In previous studies, metallosis was often excluded due to false positive results[71,79,85,90,94]. It is known that patients with a MoM articulation may develop adverse local tissue reactions (ALTR) due to metal wear debris. Even with other articulations, metal debris can be found (e.g. with taper-cup impingement or other taper related problems)[72]. Differentiating between PJI and ALTR can be challenging as patients may have elevated inflammatory parameters, peri-articular purulent appearance, falsely elevated WBC and a false positive AD LF test[72,90]. Of five false-positive AD LF tests, one was a case of metallosis. Other studies found even higher rates of metallosis among the false-positive cases,

although the numbers are small: one of three, two out of four, and three out of five[50,88,92]. One study excluded three false positive cases because of metallosis[90]. A recent Dutch study described one case of metallosis, with a negative AD LF test in a cohort of 37 patients[82]. Okroj *et al.* studied the results of AD testing in 26 cases of metallosis, and found one true positive, and eight false positive results (31%)[72]. Therefore, the value of the AD LF test in metallosis cases should be interpreted critically and with caution.

In this cohort, six patients with painful or non-functioning hip hemi-arthroplasty were included. In two of these six cases the AD LF test was positive. According to MSIS criteria, both were false positive. Using EBJIS criteria, one true positive, one false positive and one false negative were found. With the ICM 2018 criteria, one true positive and one positive in an inconclusive case were found. No other studies described AD testing of hip hemi-arthroplasties. Further studies are needed to provide guidance on AD testing for painful hip hemi-arthroplasties.

Within the scope of this study, its limitations are acknowledged. The number of patients was relatively small, and due to the retrospective design, not all measurements needed for the PJI criteria were performed. Furthermore, AD LF test was not performed in all patients that underwent aspiration, mostly due to insufficient amount of aspiration fluid or bloody fluid aspiration. Therefore, selection bias may have occurred. Although several statistical methods exist to address missing data, we believe these are more useful for big data trials than for this retrospective study[105].

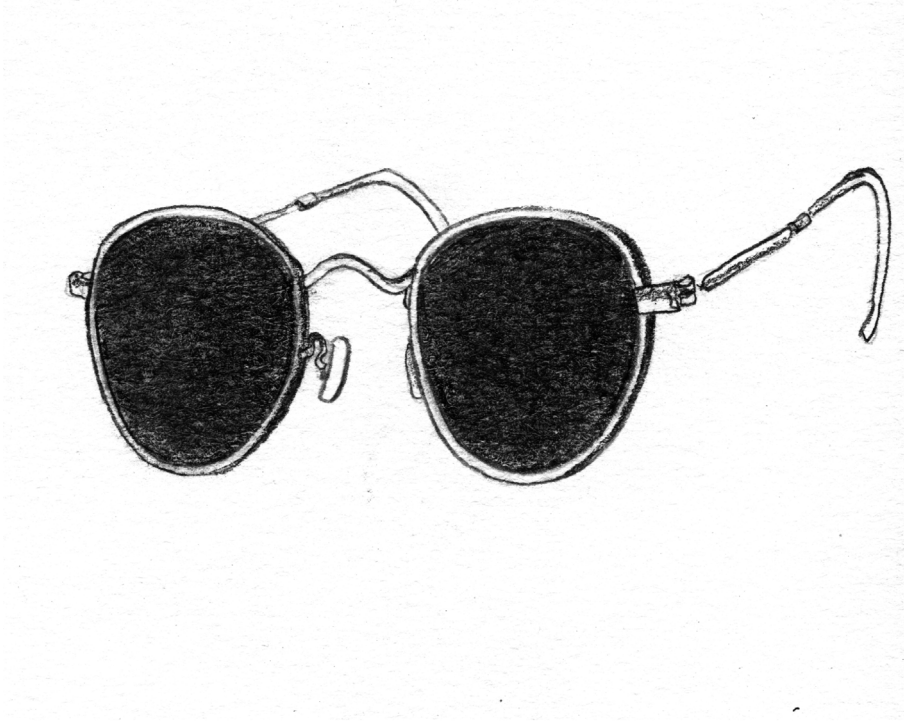
Because only hip arthroplasty patients were included in this cohort, comparison with previous studies is more difficult, as most other studies described results of both hip and knee PJI. Further research is crucial, considering the variety in sensitivity and specificity in different studies. A prospective follow-up study has already been started to evaluate the AD LF test in a larger, prospective cohort, in which a comparison to the leukocyte esterase test will also be made.

In conclusion, in a cohort of 52 patients that underwent aspiration for a painful or poor-functioning hip arthroplasty, the AD LF test had a sensitivity of 100% and specificity of 89% and an overall accuracy of 90%. Other definition criteria showed slightly different test specifics but overall accuracy was high for the EBJIS and ICM 2018 criteria as well. The AD LF test is an easy-to-use point of care test, which requires little material and can provide a quick perioperative result. This can be useful during revision surgery or when aspiration yields almost no synovial fluid. Nevertheless, caution is advised when interpreting the results, in particular when metallosis is present or possible.

DIAGNOSIS
OF PERIPROSTHETIC JOINT INFECTIONS

CHAPTER 5

Are accuracy studies for PJI diagnosis inherently flawed? And what to do with Schrödinger's hips? A prospective analysis of the alpha defensin lateral flow test in chronic painful hip arthroplasties



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CHAPTER 5

Are accuracy studies for PJI diagnosis inherently flawed? And what to do with Schrödinger's hips? A prospective analysis of the alpha defensin lateral flow test in chronic painful hip arthroplasties

Abstract

The use of the alpha-defensin (AD) lateral flow (LF) test for PJI diagnosis has been added to the most recent PJI diagnostic criteria, but previous studies usually combined hip- and knee arthroplasties. This prospective study was designed to investigate its diagnostic accuracy for PJI diagnosis in chronic painful total hip arthroplasties (THA).
Patients with chronic painful hip arthroplasties were prospectively enrolled between March 2018 and May 2020. Acute PJI or an insufficient amount of synovial fluid were exclusion criteria. For PJI diagnosis, the modified Musculoskeletal Infection Society (MSIS) criteria were primarily used. 57 patients were included in the analysis group. 38 Patients did not undergo revision surgery for different reasons (clinical group), and remain "Schrödinger's hips": cases in which PJI cannot be excluded nor confirmed until you "open the box".
The AD-LF test was positive in 9 patients and negative in 48 patients. Six patients were diagnosed with PJI. AD-LF sensitivity (MSIS criteria) was 83% (95% CI 36-100%) and specificity was 92% (95% CI 81-98%). Positive and negative predictive value were 56% and 98%, respectively.
The AD test is useful in addition to the existing arsenal of diagnostic tools, and can help the surgeon and patient in the decision-making progress. Not every patient with chronical painful THA will undergo revision surgery. Consequently, to investigate a reliable diagnostic accuracy of this test and for differential verification, a second arm of "Schrödinger's hips" should be added in in future PJI diagnostic studies.

Introduction

Periprosthetic joint infection (PJI) is one of the most severe complications after arthroplasty, with a large impact on the patient and on health care costs[8,104]. Since treatment strategies for septic prosthetic failure are considerably different than for other causes of arthroplasty failure, a correct and prompt diagnosis of PJI is of paramount importance. There is no single diagnostic test to confirm or exclude PJI. Several definitions have been proposed in the last years[8,17–20], the most commonly used being the modified MSIS criteria, which include two major and several minor sub-criteria[18] (Table 1). The recently published modified 2018 ICM (Table 2) and IBJS 2021 criteria (Table 3) have included alpha-defensin (AD), an antimicrobial peptide released by neutrophils in response to pathogens[106]. Two different AD tests are available: the enzyme-linked immunosorbent assay (ELISA) test, which has to be analyzed in a laboratory, and the lateral flow (LF) test, which has the practical advantage of providing a result within 10 minutes and can be analyzed virtually everywhere[106].

Major Criteria (PJI if at least one positive)
- Two or more positive periprosthetic cultures with phenotypically identical organisms;
- A sinus tract communicating with the joint.
Minor Criteria (PJI if at least three positive)
- Elevated serum C-reactive protein > 10 mg/L AND erythrocyte sedimentation rate > 30 mm/h;
- Elevated synovial fluid white blood cell count 3.000 cells/µL OR ++ result on leukocyte esterase test strip;
- Elevated synovial fluid polymorphonuclear neutrophil percentage (PMN%) > 80%;
- Positive histological analysis of periprosthetic tissue*;
- A single positive culture.

Table 1: Modified Musculoskeletal Infection Society (MSIS) criteria for periprosthetic joint infection (PJI)[18]; *Greater than 5 neutrophils per high-power field in 5 high-power fields observed from histologic analysis of periprosthetic tissue at 400x magnification.

Major Criteria (PJI if at least one of the following)		**Decision**
- Two positive growth of the same organism using standard culture method;		
- Sinus tract with evidence of communication to the joint or visualization of the prosthesis.		Infected
Minor Criteria (combined score ≥6: infected; 3-5: inconclusive*; <3: not infected)		**Score**
Serum:	elevated CRP (>10) or D-Dimer (>860)	2
Serum:	elevated ESR (>30)	1
Synovial:	elevated WBC count (>3000) or LE (++) or positive alpha-defensin	3
Synovial:	elevated synovial PMN (>70%)	2
Intraoperative:	single positive culture	2
Intraoperative:	positive histology**	3
Intraoperative:	positive purulence***	3

Table 2: Modified 2018 International consensus meeting (ICM) criteria for chronic periprosthetic joint infection (PJI); CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; WBC: white blood cells; LE: leukocyte esterase; PMN: polymorphonuclear neutrophils; *Consider further molecular diagnostics such as Next-Generation Sequencing; **Greater than 5 neutrophils per high-power field in 5 high-power fields observed from histologic analysis of periprosthetic tissue at 400x magnification; ***No role in suspected adverse local tissue reaction.

As differences in diagnostic accuracies between various joints have been reported[106,107], a recent meta-analysis reported sensitivity and specificity for THA separate from TKA: pooled sensitivity for THA PJI diagnosis using the LF test was 80%, and specificity 92%, slightly lower than its accuracy for TKA (87% and 96%, respectively)[106]. In literature, no previous prospective study investigated the diagnostic accuracy of the AD-LF test for PJI diagnosis exclusively in chronic painful hip arthroplasties. The SWAG study (Synovasure and White blood cell count after Aspiration compared to the Gold standard) was designed to prospectively evaluate the diagnostic performance of AD-LF testing in this challenging (and heterogenous) patient group. The aim was to answer the following questions:

1) What is the sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) for PJI diagnosis of the AD-LF test for chronic painful THA?

2) Which subgroups can be identified in which AD-LF testing is more (or less) accurate (e.g., metallosis)?

	Infection Unlikely (all findings negative)	Infection Likely (two positive findings)[a]	Infection Confirmed (any positive finding)
Clinical features	Clear alternative reason for implant dysfunction (e.g., fracture, implant breakage, malposition, tumor)	1) Radiological signs of loosening within the first five years after implantation 2) Previous wound healing problems 3) History of recent fever or bacteremia 4) Purulence around the prosthesis[b]	Sinus tract with evidence of communication to the joint or visualization of the prosthesis
Serum C-reactive protein		> 10 mg/l (1 mg/dl)[c]	
Synovial leukocyte count[c] (cells/µl)	≤ 1,500	> 1,500	> 3,000
PMN (%)[c]	≤ 65%	> 65%	> 80%
Alpha-defensin[e]			Positive immunoassay or lateral flow assay[e]
Aspiration fluid cultures[f]		Positive culture of aspiration fluid	
Intraoperative cultures (fluid and tissue)[f]	All cultures negative	Single positive culture[g]	≥ two positive samples with the same microorganism
Sonication cultures[f,h] (CFU/ml)	No growth	> 1 CFU/ml of any organism[g]	> 50 CFU/ml of any organism
Histology[c,i] in high-power field (400x magnification)	Negative	Presence of ≥ five neutrophils in a single HPF	Presence of ≥ five neutrophils in ≥ five HPF or presence of visible microorganisms
Nuclear imaging	Negative three-phase isotope bone scan[c]	Positive WBC scintigraphy[j]	

Table 3: European Bone and Joint Infection Society (EBJIS) criteria for periprosthetic joint infection (PJI)[22]; PMN: polymorphonuclear neutrophils; CFU: colony forming units; HPF: high power field; WBC: white blood cell count; summary key:

a. Infection is only likely if there is a positive clinical feature or raised serum C-reactive protein (CRP), together with another positive test (synovial fluid, microbiology, histology or nuclear imaging).
b. Except in adverse local tissue reaction (ALTR) and crystal arthropathy cases.
c. Should be interpreted with caution when other possible causes of inflammation are present: gout or other crystal arthropathy, metallosis, active inflammatory joint disease (e.g., rheumatoid arthritis), periprosthetic fracture, or the early postoperative period.
d. These values are valid for hips and knee PJI. Parameters are only valid when clear fluid is obtained and no lavage has been performed. Volume for the analysis should be > 250 µL, ideally 1 ml, collected in an EDTA (ethylenediaminetetraacetic acid) containing tube and analyzed in <1h, preferentially using automated techniques. For viscous samples, pre-treatment with hyaluronidase improves the accuracy of optical or automated techniques. In case of bloody samples, the adjusted synovial WBC = synovial WBC $_{observed}$ – [WBC $_{blood}$ / RBC (red blood cell count)$_{blood}$ x RBC $_{synovial\ fluid}$] should be used.
e. Not valid in cases of ALTR, hematomas, or acute inflammatory arthritis or gout.
f. If antibiotic treatment has been given (not simple prophylaxis), the results of microbiological analysis may be compromised. In these cases, molecular techniques may have a place. Results of culture may be obtained from preoperative synovial aspiration, preoperative synovial biopsies or (preferred) from intraoperative tissue samples.
g. Interpretation of single positive culture (or < 50 CFU/ml in sonication fluid) must be cautious and taken together with other evidence. If a preoperative aspiration identified the same microorganism, they should be considered as two positive confirmatory samples. Uncommon contaminants or virulent organisms (e.g., Staphylococcus aureus or Gram-negative rods) are more likely to represent infection than common contaminants (such as coagulase-negative staphylococci, micrococci, or Cutibacterium acnes).
h. If centrifugation is applied, then the suggested cut-off is 200 CFU/ml to confirm infection. If other variations to the protocol are used, the published cut-offs for each protocol must be applied.
i. Histological analysis may be from preoperative biopsy, intraoperative tissue samples with either paraffin, or frozen section preparation.
j. WBC scintigraphy is regarded as positive if the uptake is increased at the 20-hour scan, compared to the earlier scans (especially when combined with complementary bone marrow scan).

Methods

This single center prospective cohort study was performed in a large secondary teaching hospital and PJI referral center for the region. Approval for the study was given by the in-hospital ethics committee in February 2018 (number: L-018-009).

Patients

Adult patients that underwent joint aspiration as part of the diagnostic work-up for evaluation of painful or poorly functioning total hip arthroplasty (THA) between March 2018 and May 2020 were included in a prospective database. A total of 151 consecutive patients underwent joint aspiration during this period. Exclusion criteria for this study were: suspicion of an acute PJI (joint aspiration performed within 3 months of index surgery), insufficient amount of fluid for AD testing (dry tap, <1 cc), and aspiration performed after resection arthroplasty. A priori, antibiotic use and suspected metallosis were not exclusion criteria. Data on aspirations done for painful hip hemi-arthroplasties (HHA) were collected separately. PJI was defined using the modified MSIS criteria[18]. For comparison purposes, the modified 2018 ICM criteria[20] and latest EBJIS criteria were also described[22].

Intervention

Hip aspiration was performed in the operating room (OR) under sterile conditions with the use of fluoroscopy. After this, a (temporary) diagnosis was made and patients were selected for aseptic revision, septic two-stage revision, wait-and-see policy or antibiotic suppression therapy. If there was suspicion of PJI, two-stage revision was performed. If the results indicated aseptic pathology, either one-stage revision was performed or - in subclinical or improving patients - a wait-and-see policy was started. In high-risk patients in terms of substantial co-morbidities with suspicion or evident PJI, antibiotic suppression therapy was considered. During revision surgery, six tissue cultures were collected. Samples were cultured for at least 14 days.
The patient's history, clinical findings, laboratory tests including serum C- reactive protein (CRP), Erythrocyte Sedimentation Rate (ESR), White Blood Cell count (WBC) and results of synovial tests from joint aspiration were documented. The AD-LF test (Synovasure®, Zimmer Biomet, Warsaw, Indiana, USA) was performed according to manufacturer guidelines. If a sufficient amount of synovial fluid was obtained, the remaining fluid was used for culture in blood culture bottles (aerobic and anaerobic), white blood cell count (WBC) and polymorphonuclear neutrophil percentage (PMN%), and leukocyte esterase (LE) dipstick testing.

Statistical analysis

Sensitivity, specificity, PPV and NPV of the AD-LF test were calculated in the group that underwent revision surgery. Except for age, the scale variables were described using the median and the range regarding a non-normal distribution measured by means of the one-sample Kolmogorov-Smirnov test. 95% Confidence intervals (CI) were calculated and are described.

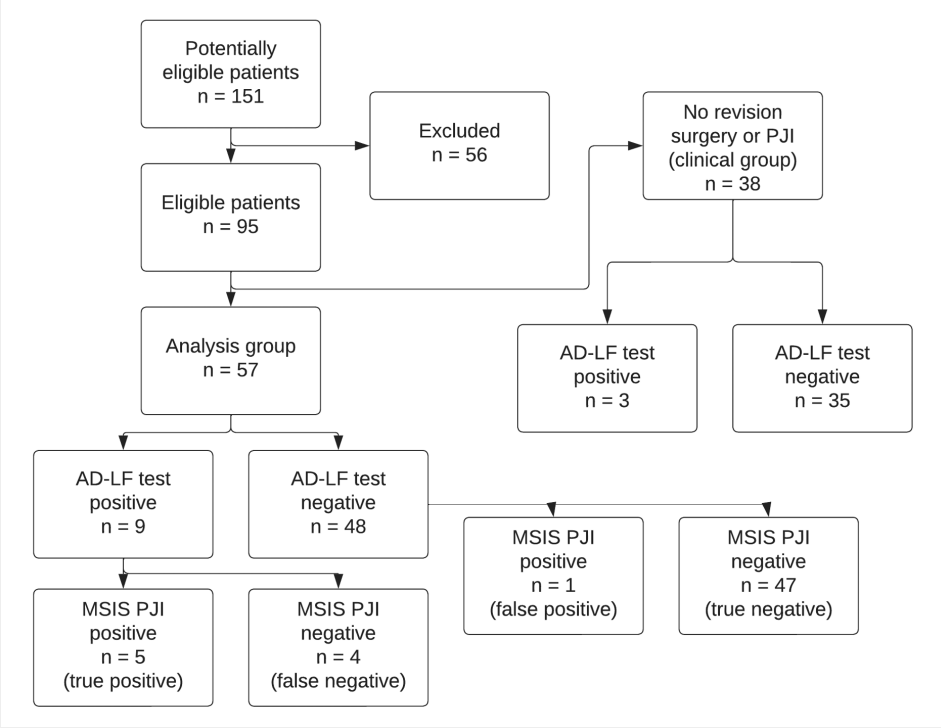


Figure 1: Flowchart of patients, index test and reference standard. AD-LF: alpha-defensin lateral flow; MSIS: Musculoskeletal Infection Society criteria for periprosthetic joint infection (PJI) diagnosis.

Results

151 Patients underwent aspiration of hip arthroplasty, of which 56 patients were excluded. Exclusion criteria were hip hemi-arthroplasty (n = 9), acute PJI (n = 5), or an insufficient amount of synovial fluid to perform the AD test (n = 42). 95 Aspirations of THA were included. These were split in two groups: the analysis group, with sufficient data to confirm or rule out PJI, and the clinical group: patients that did not meet criteria for PJI diagnosis, but who did not undergo surgery and therefore remain cases where PJI cannot be excluded. See Figure 1 for a flowchart.

57 THA aspiration cases were included in the analysis group: 55 patients underwent hip revision surgery (7 positive AD tests), and 2 patients treated with suppression had definitive PJI. Both had a positive AD test, and were the only patients in the cohort with a positive culture of aspiration fluid (Staphylococcus epidermidis in both cases). Characteristics can be found in Table 4. No patients were on antibiotics prior to, or at the time of, aspiration. Intraoperative cultures demonstrated positive cultures in nine patients. Histology was positive in three cases (of 27 cases with histology performed). Three patients had

	Analysis group (median and range, or occurrence) n=57	Clinical group (median and range, or occurrence) n=38
Demographics		
Age (years)	71.0 (mean: 69.9, range 38 – 89)	74.5 (mean: 71.2, range 49 – 90)
Sex: male	n=17	n=12
Sex: female	n=40	n=26
ASA: I	n=1	n=0
ASA: II	n=40	n=15
ASA: III	n=15	n=14
ASA: IV	n=1	n=1
ASA: unknown	n=0	n=8
BMI (kg/m^2)	26.8 (21.4 – 34.6)	28.0 (21.4 – 42.0)
Deceased	n=0	n=0
Initial operation		
Time interval after THA implantation (months)	69 (4 – 587)	31 (5 – 232)
Primary THA	n=35	n=33
Revision THA	n=22	n= 5
Cemented / Hybrid	n=21	n=10
Uncemented	n=36	n=28
Metal on metal	n=3	n=2
Blood tests		
CRP (mg/L)	2.7 (1 – 25) (n=48)	4.4 (1 – 171) (n=34)
ESR (mm/hr)	11.0 (2 – 94) (n=43)	14.5 (2 – 115) (n=32)
WBC (/nL)	7.1 (4.1 – 12.4) (n=47)	7.4 (3.6 – 11.6) (n=33)
Aspiration results		
1/ AD test	**n=57**	**n=38**
AD-LF test: negative	n=48	n=35
AD-LF test: positive	n=9	n= 3
2/ Aspiration cultures	**n=52**	**n=33**
Aspiration culture positive	n=2	n=0
3/ WBC count	**n=52**	**n=31**
WBC Count: < 3000	n=40	n=23
WBC Count: > 3000	n=12	n=8
PMN % > 80	n=6	n=4
4/ LE test	**n=36**	**n=21**
LE Test: negative	n=10	n=1
LE Test: trace	n=17	n=15
LE Test: 1+	n=2	n=3
LE Test: 2+	n=3	n=2
LE Test: 3+	n=1	n=0
LE Test: unreadable	n=3	n=0
Intraoperative tests		
Cultures	**n=54**	
Two or more positive	n=1	
One positive	n=9	
Negative	n=44	
Histology	**n=27**	
Positive	n=3	
Negative	n=24	

Table 4: Patient, initial operation and test characteristics; ASA: American Society of Anesthesiologists score; BMI: Body Mass Index; THA: Total Hip Arthroplasty; CRP: C-reactive protein; ESR: Erythrocyte Sedimentation Rate; WBC: White Blood Cell count; AD-LF: alpha-defensin lateral flow; PMN%: polymorphonuclear neutrophil percentage; LE: leukocyte esterase; AD: alpha-defensin).

	Analysis group			Clinical group		
	Work up: PJI confirmed (fistula or 3 MSIS minor criteria)	Work up: PJI suspected (1-2 MSIS minor criteria	Work up: PJI not suspected (0 MSIS minor criteria)	Work up: PJI confirmed (fistula or 3 MSIS minor criteria)	Work up: PJI suspected (1-2 MSIS minor criteria	Work up: PJI not suspected (0 MSIS minor criteria)
N:	2	14	41	0	16	22
Blood tests						
CRP >10 mg/L	1 (median: 15)	0 (median: 2)	4 (median: 2.7)		5 (median: 7)	3 (median: 3.8)
ESR >30 mm/hr	1* (94)	1 (median: 7.5)	3 (median: 11)		6 (median: 20)	1 (median: 9)
Aspiration						
AD-LF +	2	5	2 (dubious)		2	1 (MoM)
WBC > 3000 cells/µl	1* (87,000)	11 (median: 5500)	0 (median: 1200)		8 (median: 3100)	0 (median: 1600)
PMN% > 80%	1* (97%)	5 (median: 77)	0 (median: 30)		4 (median: 59)	0 (median: 28)
LE ++	1*	3	0		2	0
Blood culture +	2	0	0		0	0
Treatment / Diagnosis	Suppression: 2	Two-stage: 7 One-stage: 7	One-stage: 41		Suppression: 1† Extra-articular pathology: 11 No diagnosis, clinically better in time: 4	Extra-articular pathology: 13 No diagnosis, clinically better in time: 9
Intraoperative						
Cultures	-	> 2 positives: 1 1 positive: 2	> 2 positives: 0 1 positive: 6			
Histology +	0	3	0			
PJI confirmed postoperatively	2 (2/2 AD pos)	4 (3/4 AD pos)	0			

Table 5: Comparison of aspiration and intra-operative results between the analysis group (in which periprosthetic joint infection (PJI) could be confirmed or ruled out) and the clinical group (PJI nor confirmed nor ruled out, but treated according to symptoms); *: only performed in 1 case; †: pragmatic treatment based on microorganisms found in DAIR (debridement, antibiotics, irrigation and implant retention) procedure three years prior to inclusion; MSIS: Musculoskeletal Infection Society; CRP: C-reactive protein; ESR: Erythrocyte Sedimentation Rate; WBC: White Blood Cell count; AD-LF: alpha-defensin lateral flow; MoM: metal-on-metal; PMN%: polymorphonuclear neutrophil percentage; LE: leukocyte esterase; AD: alpha-defensin.

	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)	Accuracy (95% CI)
MSIS									
All patients	5	4	1	47	83% (36-100)	92% (81-98)	56% (31-77)	98% (89-100)	91% (81-97)
Modified 2018 ICM									
1: All patients (inconclusive treated as infected)	9	0	8	40	53% (28-77)	100% (91-100)	100%	83% (75-89)	86% (74-94)
2: All patients (inconclusive treated as non-infected)	6	3	1	47	86% (42-100)	94% (83-99)	67% (39-86)	98% (88-100)	93% (83-98)
3: Exclusion of 'inconclusive' results	6	0	1	40	86% (42-100)	100% (91-100)	100%	98% (87-100)	98% (89-100)
EBJIS									
1: All patients (likely treated as infected)	9	0	11	37	45% (23-68)	100% (91-100)	100%	77% (69-83)	81% (68-90)
2: Exclusion of 'likely' results	9	0	10	37	47% (24-71)	100% (91-100)	100%	79% (71-85)	82% (70-91)

Table 6: Diagnostic accuracy of alpha-defensin lateral flow test for total hip arthroplasty.; MSIS: Musculoskeletal Infection Society; ICM: International Consensus Meeting; EBJIS: European Bone and Joint Infection Society; TP: true positive; FP: false positive; FN: false negative; TN: true negative; CI: confidence intervals; PPV: positive predictive value; NPV: negative predictive value.

metallosis: one with a positive AD-LF test, diagnosed with PJI, and two not-infected with a negative AD-LF test. The clinical group consisted of 38 patients who did not undergo surgery because of subclinical aseptic loosening with decreasing pain/wait-and-see policy (n= 15) or aseptic loosening excluded / other diagnosis than PJI (n= 23). All were excluded for AD test performance analysis. In this clinical group, three patients had a positive AD-LF test, one of which had metallosis. Differences in results of aspiration and intra-operative tests between the analysis group and the clinical group can be found in Table 5.
In the analysis group, AD-LF sensitivity (MSIS criteria) was 83% (95% CI 36-100%) and specificity was 92% (95% CI 81-98%). PPV and NPV were 56% and 98%, respectively. See Table 6 for number of true positives (TP), false positives (FP), false negatives (FN) and true negatives (TN) and a comparison with the other diagnostic criteria.

Discussion

In this prospective study of patients with chronic painful THA we evaluated the results of the AD-LF test, and found sensitivity and specificity to be comparable to other reports on the AD-LF test[106]. To our knowledge, this is the first prospective study investigating the AD-LF test exclusively for hip arthroplasty, which is important, because hip and knee PJI are probably not exactly the same[106]. For example, in this study, a quarter of all aspirated patients had to be excluded because of an insufficient amount of fluid; in our experience, such “dry taps” are more common in hips, compared to knee aspirations.

Furthermore, the clinical group in this study reflects the decisions and uncertainties of daily orthopedic practice: not all chronic painful THAs remain painful and warrant revision, especially if the diagnostic workup does not confirm PJI.

Question 1: What is the sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) for PJI diagnosis of the AD-LF test for chronic painful THA?
In the analysis group, AD-LF sensitivity (MSIS criteria) was 83% (95% CI 36-100%) and specificity was 92% (95% CI 81-98%). PPV and NPV were 56% and 98%, respectively. The modified MSIS criteria were used to define PJI[18]. It is obvious that the other two criteria described render different numbers for (mainly) test sensitivity, because more cases are considered (possibly) infected. Using the modified 2018 ICM criteria, unfortunately, many cases were considered ‘inconclusive’. These cases were neither definitively infected nor not infected, but excluding them would be a form of bias. We therefore chose to report the numbers considering these cases as infected, as not infected and excluding them. Using the EBJIS criteria and 2018 ICM criteria, there is another caveat: the alpha defensin test is the studied test, but also part of the definition. Thus, a positive AD test leads to easier fulfilment of the definition “infected”. This positive feedback is a form of bias, causing fewer false positive test results.
In the last decade PJI definitions have been revised and now contain more criteria on which PJI can be diagnosed. The categories “inconclusive” (2018 ICM) or “infection

likely" (EBJIS 2021) were added, it seems, to make it less likely that we incorrectly state that PJI is absent. But not every chronic painful THA will (or should) be revised. With the current PJI definitions, a PJI cannot be excluded without intra-operative cultures and histology. Since (multiple) positive intra-operative cultures lead to a positive diagnosis of PJI in each definition used, these hips can be thought of as "Schrödinger's hips". They are infected and not-infected at the same time but we can't be sure until we "open the box". These "Schrödinger's hips" remain an uncertain factor, leading to bias. To our knowledge, most of the diagnostic performances of PJI tests have been investigated with this bias. Differential verification might be a solution for this problem. Differential verification is the use of different reference standards between patients[108]. One reference standard could be the modified MSIS PJI criteria for patients who are revised (so a complete reference standard is present in these patients), while the other reference standard could be long-term follow-up for patients selected for a "wait-and-see" approach. With this, one would expect the long-term follow-up to identify the PJI patients in the cohort eventually, and so the follow-up is used as a proxy to obtain information of true status at the moment of the studied test.

Question 2: Which subgroups can be identified in which AD-LF testing is more (or less) accurate (e.g., metallosis)?

Several studies concluded that presence of metallosis could be a misleading factor and increase the likelihood of false-positive AD results[50,72,88,93]. Of the three patients with a MoM THA in the analysis group, one result was false positive (MSIS not infected, 2018 ICM inconclusive due to positive AD test and EBJIS infected due to positive AD test) and two were true negative. So, although being a very small subgroup, one out of three patients with MoM in this study had false positive results. Our advice would be to refrain from using the AD test for MoM patients in the diagnostic workup of chronic painful hip arthroplasties, at least until larger MoM groups have been studied.

A second possible variable is the administration of antibiotics before performing the AD-LF test. The best available evidence concluded that the administration of antibiotics does not decrease the AD level in synovial fluid[71]. Antibiotic use was not an exclusion criterion in this study, but none of the included patients were treated with antibiotics in the weeks prior to aspiration.

During the study period, nine patients with a hip hemi-arthroplasty underwent aspiration and AD testing. All nine were negative (six underwent revision surgery and were definitely true negative), but unfortunately this sample size was too small to draw any conclusions. Two patients demonstrated a doubtful positive AD-LF test (Figure 2). Both patients had WBC counts of 2000-2500 cells/μL. This study is the first in literature to describe cases with such a doubtful positive test. After consulting the manufacturer, the authors decided to consider both AD tests as positive for PJI. For both cases, a one-stage revision was performed, including a very thorough debridement. Both cases were not infected according to the modified MSIS criteria, and were only considered infected using the 2018 ICM criteria (1/2, the other being inconclusive) and EBJIS criteria (2/2) because of these positive AD tests. When the doubtful AD-LF test was considered negative, these

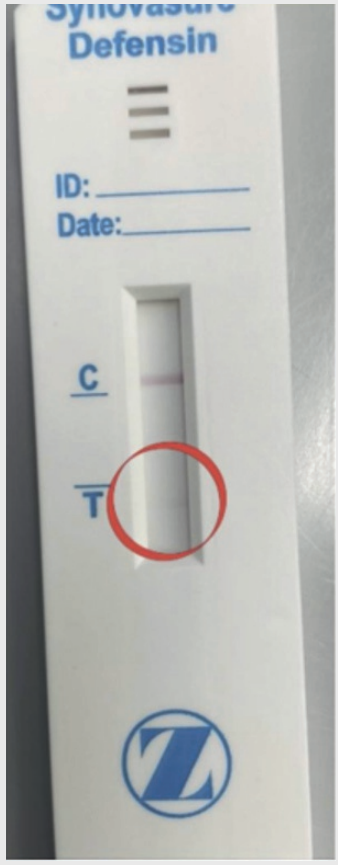


Figure 2: Example of a doubtful positive alpha-defensin lateral flow test (Synovasure®, Zimmer Biomet, Warsaw, Indiana, USA).

borderline cases would be not infected and inconclusive, respectively (2018 ICM criteria), and likely but not confirmed (EBJIS), demonstrating the bias we anticipated in advance. If borderline test results are the only sign of infection, they should be regarded with caution and be used as "guide value" rather than "cut-off value". If revision in these cases is indicated, apart from the test results, a one-stage revision with thorough debridement and intra-operative cultures and histology could be considered, especially since finding positive cultures during revision surgery is not associated with inferior survival in the short-term (up to two years)[109]. If revision is not indicated, follow-up or repeat aspiration would be an alternative approach.

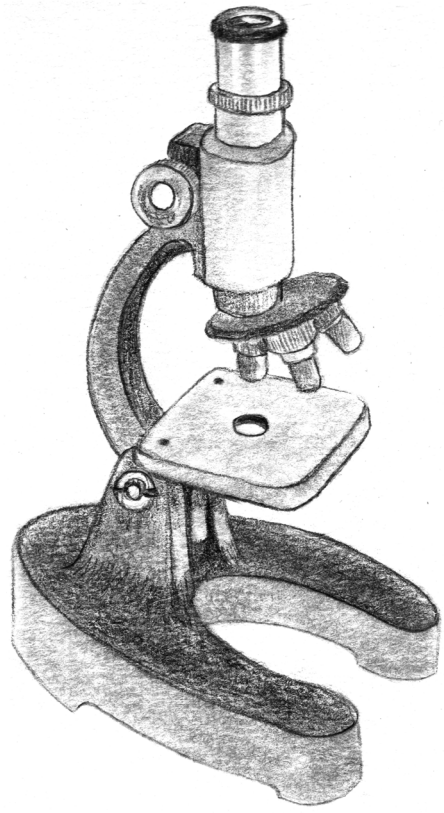
The main caveat of this study is that not all possible tests were performed in every patient: due to the hospital infrastructure, histology was not performed in all cases, and sonication was not possible. Because of low yields, in some cases the LE test was not performed. Furthermore, due to the patient centered design of this study, not all patients underwent revision surgery. We should be aware that selecting the revision cases does introduce bias. If, understandably, such a selection is made, we advise to use follow-up or repeat aspirations as the second arm for differential verification of these "Schrödinger's hips", to ultimately find the true accuracy of diagnostic tests in PJI and their role in the diagnostic work up of chronic painful arthroplasties.

The AD test is a useful addition to the arsenal of tests available for PJI diagnosis, and can help the surgeon and patient in the decision-making progress. We suggest incorporating differential verification for PJI test accuracy studies in groups of painful arthroplasties, because not all patients will undergo revision surgery. All patients with a positive index test are verified by one reference standard (PJI definition) and all negative patients are verified by a second reference standard (follow-up or repeat aspirations).

TREATMENT
OF PERIPROSTHETIC JOINT INFECTIONS

CHAPTER 6

The novel endolysin XZ.700 effectively treats MRSA biofilms in two biofilm models without showing toxicity on human bone cells in vitro



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CHAPTER 6

The novel endolysin XZ.700 effectively treats MRSA biofilms in two biofilm models without showing toxicity on human bone cells in vitro

Abstract

In this *in vitro* study the effect of XZ.700, a new endolysin, on Methicillin Resistant *Staphylococcus aureus* (MRSA) biofilms grown on titanium was evaluated. Biofilms of *S. aureus* USA300 were grown statically and under flow, and treatment with XZ.700 was compared to povidone-iodine (PVP-I) and gentamicin. To evaluate cytotoxic effects of XZ.700 and derived biofilm lysates, human osteocyte-like cells were exposed to biofilm supernatants, and metabolism and proliferation were quantified.
XZ.700 showed a significant, concentration dependent reduction in biofilm viability, compared to carrier controls. Metabolism and proliferation of human osteocyte-like cells was not affected by XZ.700 or lysates, unlike PVP-I and gentamicin lysates which significantly inhibited proliferation. Using time-lapse microscopy, rapid biofilm killing and removal was observed for XZ.700. In comparison, PVP-I and gentamicin showed slower biofilm killing, with no apparent biofilm removal.
In conclusion, XZ.700 reduces MRSA biofilms, especially under flow condition, without toxicity for surrounding bone cells.

Introduction

Periprosthetic joint infection and other biofilm-associated infections, such as infections of mechanical heart valves, vascular endoprostheses and pacemakers, are major complications after surgery, burdening the patient and the hospital with prolonged intravenous antibiotic treatment and multiple surgical procedures[8,11,104]. The costs of such infections put a strain on the health care system[7]. Most of these infections are caused by *Staphylococcus spp,* with *Staphylococcus aureus* being a prominent species[110]. *S. aureus* is known to extensively form biofilms, i.e. structured microbial communities embedded in a matrix of polymeric substances[111]. Bacteria within biofilms are protected against antimicrobial therapy and the host immune system; biofilm formation causes treatment resistance and enhances the development of antibiotic resistant strains[112]. Surgical therapy for periprosthetic joint infection is focused on macroscopic removal of infected tissue and biofilm, i.e. (partial) exchange of arthroplasty components, rigorous tissue removal, and extensive irrigation with saline. Local antimicrobial therapy, such as irrigation with antibiotics or povidone-iodine (PVP-I) or implantation of antibiotic-releasing material can be used in addition to surgical removal, but currently, no local therapy exists that has been proven sufficiently effective to be implemented in clinical guidelines[113–115].

With the worldwide rise of antibiotic-resistant microorganisms, recent studies have focused on alternative treatment modalities, that are less prone to resistance, such as

light therapy, bacteriophages, and endolysins[26]. Endolysins are cell wall hydrolyzing enzymes that are produced by bacteriophages, and cause cell death to specific bacterial species, while other species are not killed[116,117]. Their use in fighting biofilm-associated infections is promising, as several endolysins have been shown to significantly reduce numbers of *S. aureus* in biofilms *in vitro*[118–122].

XZ.700 is a chimeric endolysin built combining parts of S. aureus bacteriophage endolysin Ply2638[123] and Lysostaphin[124]. The enzymatic cleavage of the staphylococcal cell wall by XZ.700 is dependent on both, the recognition of the cell wall by a cell wall-binding domain (with SH3b homology), and by the specific hydrolytic activity of the two enzymatically active domains (an amidase and an endopeptidase). XZ.700 is produced as a recombinant protein in a microbial expression system.

The current study was designed to study the efficacy and safety of XZ.700 endolysin against *S. aureus* biofilms *in vitro*. *S. aureus* biofilms were grown on titanium discs *in vitro* in the previously described *Amsterdam Active Attachment* (AAA) biofilm model (static model)[125,126]. Effectiveness of XZ.700 endolysin was determined by the reduction in colony forming units (CFU/mL) following several treatment strategies (e.g., dose-response and time-response), compared to standard of care treatments (povidone-iodine and gentamicin). To assess if breaking extracellular DNA bonds in the biofilm would enhance the effect of XZ.700, the combined effect with DNAse was tested. In addition, a microfluidics-based biofilm model (flow model) was applied to mimic flow-based treatment strategies[126]. Finally, cytotoxicity of endolysin and endolysin-treated biofilms was tested using human osteocyte-like cells.

Methods

Bacterial strains and culture

Methicillin-resistant *S. aureus* (MRSA) strain USA300[127] was routinely cultured at 37°C on tryptic soy agar (TSA) plates or in tryptic soy broth (TSB). To allow visualization of *S. aureus* by microscopy in the flow model, *S. aureus* USA300 was transformed with plasmid pMV158-GFP carrying a gene for green fluorescent protein (GFP)[128,129]. Successful transformants were selected and maintained on TSA plates containing 2 µg/mL tetracycline.

Antibiotics

Endolysin XZ.700 was supplied by Micreos (Bilthoven, The Netherlands), and diluted to a solution of 250 µg/mL in phosphate buffered saline (PBS, containing NaCl 8 g/L, KCl 0.2 g/L, Na_2HPO_4 1 g/L, KH_2PO_4 0.2 g/L) with the addition of 0.1% bovine serum albumin (BSA; Sigma-Aldrich, St. Louis, MO, USA). Povidone-iodine (PVP-I; AddedPharma, Oss, The Netherlands) at 0.35% (3.5 µg/mL)[114], and gentamicin (Sigma-Aldrich, St. Louis, MO, USA) at 1000 µg/mL, comparable to the tissue concentration when using

local gentamicin[130,131], were prepared in PBS from stock solutions containing 10% PVP-I and 50 mg/mL gentamicin, respectively.

Static biofilm model

Biofilms were grown in half strength TSB supplemented with 0.25% (w/v) D-glucose. The inoculum was prepared by diluting an overnight culture of *S. aureus* USA300 grown in TSB 1:50 in half strength TSB containing 0.25% (w/v) D-glucose. The stainless-steel lid of the AAA-model was fitted with titanium discs (diameter 9.52 mm, thickness 1.1 mm) and sterilized by autoclaving as described previously[125,126]. Each well of a sterile 24 well plate was filled with 1 ml inoculum and incubated for 8 h at 37°C to allow for adhesion of *S. aureus* to the titanium surfaces. Subsequently the medium was refreshed once for the 24 h old biofilms and following a 16 h - 8 h - 16 h regime until 48 h biofilms were obtained. After exposure to XZ.700 and control treatment agents (PVP-I and gentamicin) for 4 hours (or shorter in experiments with different exposure times), the discs were irrigated with PBS, vortexed, and sonicated twice for 50 s (1 s on, 1 s off to prevent overheating, turning the disc after the first 50 s) at 20 kHz and 40% amplitude of 130 W with a probe sonicator (Sonics Vibracell VC130, Newtown, CT, USA). The number of residual viable bacteria was determined upon serial dilution and plating on TSA. All tests were performed in triplo or quadruplo and on two separate occasions.

Flow biofilm model

Biofilms were formed under flow-conditions using the Bioflux Z1000 (Fluxion Biosciences, San Francisco, CA, USA) setup[126]. The Bioflux was inoculated with GFP-expressing *S. aureus* USA300. A biofilm was allowed to grow for 16 h under constant medium flow (medium: half strength TSB + 0.25% (w/v) glucose + 2 µg/mL tetracycline (Sigma-Aldrich, St. Louis, MO, USA); pressure: 0.4 dyne/cm^2). After 16 h of biofilm growth, the biofilms were exposed to XZ.700 (12.5, 25 and 50 µg/mL), PVP-I 0.35% or gentamicin 1000 µg/mL, supplemented with 0.5 µL/mL propidium iodine (PI) to assess cell death. The treatment solutions were supplied at a pressure of 0.4 dyne/cm^2. The effect of the different agents on the biofilm in terms of decrease in green fluorescence and increase in PI fluorescence was visualized with time-lapse microscopy, taking images with a 10x objective of two selected positions per channel every 2.5 min for 4 h, using brightfield and fluorescence (FITC) filters acquisition. Videos showing changes in fluorescence of treated and untreated controls were constructed after addition of a timestamp and a scale bar using image analysis software (ImageJ, version 1.52, W. Rasband, National Institutes of Health, Baltimore, MD, USA). Except for image cropping, no image modification was performed.

Cytotoxicity, cell metabolic activity, and proliferation

The supernatants obtained in the static model comparing XZ.700 (12.5, 25 and 50 µg/mL) with PVP-I (0.35%) and gentamicin (1000 µg/mL) were used for subsequent toxicity testing, hypothesizing that not only the agent, but also the debris of lysed cells and bacteria, including bacterial toxins, have an effect on surrounding cells in vivo. Brief-

ly, human osteocyte-like cells were obtained as outgrowth from collagenase-stripped pieces (1-3 mm) of human bone, obtained as surgical waste material from elective hip or knee surgery (Ethical Review Board of the VU Medical Center, Amsterdam, The Netherlands, protocol number 2016/105). Donors were adult males and females, without metabolic bone disease. No further data about the donors is available. Cells from 5 donors were pooled to obtain more repeatable results, representative of multiple individuals. Cells were cultured up to passage 5, released by incubation with 0.25% trypsin (Gibco, Invitrogen, Waltham, MA, USA), and 0.1% ethylene-diamine-tetra-acetic acid (Merck, Darmstadt, Germany) in PBS, and seeded at 20.000 cells/cm^2 in 48-wells plates (Greiner Bio-One, Kremsmuenster, Austria). Cells were left to adhere for 24h in culture medium consisting of Minimum Essential Medium Alpha modification (α-MEM, Thermo Fisher Scientific, Eugene, OR, USA) supplemented with 10% HyClone FetalClone1 (FC1, Thermo Fisher Scientific) and 1% penicillin, streptomycin, and fungizone-mix (PSF; Sigma, Saint Louis, MO, USA). After cell attachment the cells were washed and subsequently exposed to the supernatants (50% supernatant, 50% fresh culture medium without PSF) for 48 h. Seven controls were added: 100% cell culture medium, and the six different supernatants without biofilm exposure (50% in culture medium). AlamarBlue (Thermo Fisher Scientific) was added for analysis of metabolic activity. After 48h incubation the fluid was analyzed using a Synergy HT® spectrophotometer for quantification of AlamarBlue conversion (fluorescence was read in the samples at 530 nm excitation and 590 nm emission). Subsequently, the wells were emptied, 200 µL sterile water was added, cells were lysed by freezing and thawing three times, and total cell DNA was assessed using the Cyquant Cell Proliferation Assay (Molecular Probes, Eugene, OR, USA) according to the manufacturers' instructions (fluorescence was read in the samples at 480 nm excitation and 520 nm emission with a Synergy HT® spectrophotometer), to evaluate cell number.

Statistical analysis

Statistical analysis was performed using IBM SPSS version 23 (IBM, Armonk, NY, USA). Analysis of variance (ANOVA) and Tukey multiple range test were used to test differences between groups. Values of $p<0.05$ were considered statistically significant.

Results

Effect of XZ.700 on MRSA biofilms in a static model

Dose dependent effect: After biofilm development for 24 and 48 h, the biofilm-containing titanium discs were immersed in serially diluted concentrations of XZ.700 (6.25-400 µg/mL) and a carrier control, for 4 h. For the 24 h-old biofilms, maximum biofilm reduction of 80-90% was obtained at concentrations between 6.25-50 µg/mL. Higher concentrations of XZ.700 did not result in higher killing; in contrast, the remaining viability after treatment with high concentrations was higher compared to the lower concentrations. No significant reduction was seen for the 48 h-old biofilms (Figure 1).

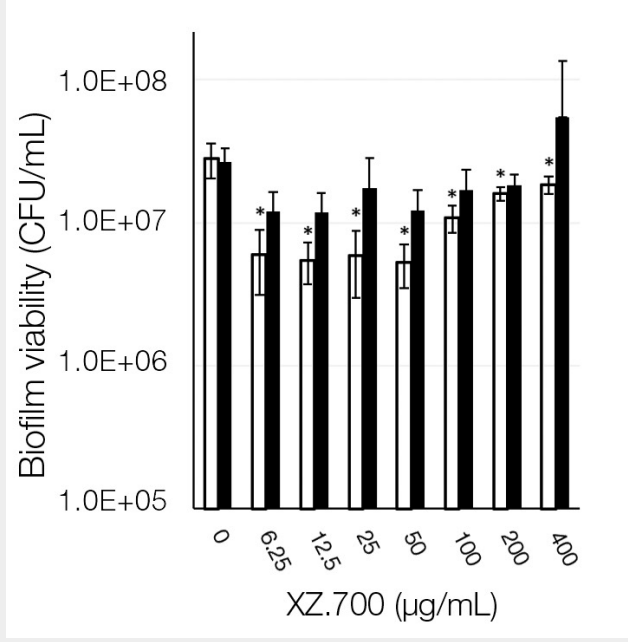


Figure 1: Dose-dependent effect of 4 h exposure of XZ.700 on the viability of 24 h (white bars) and 48 h (black bars) old MRSA biofilms; *Significant reduction in biofilm viability compared to control, p<0.05; MRSA: methicillin resistant Staphylococcus aureus.

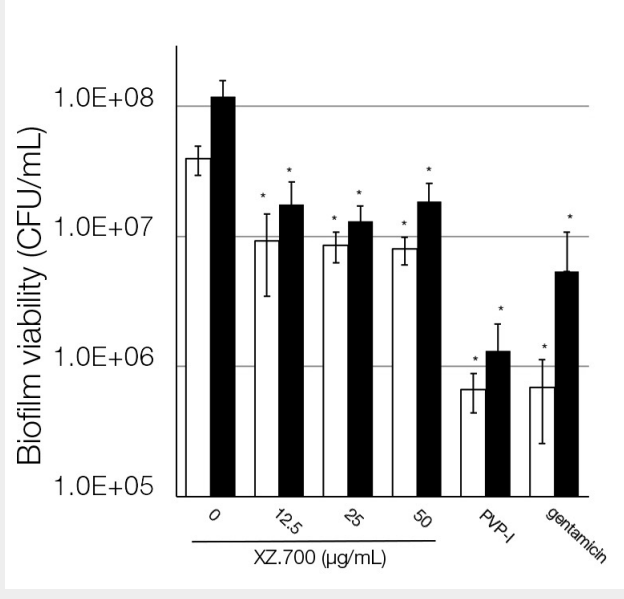
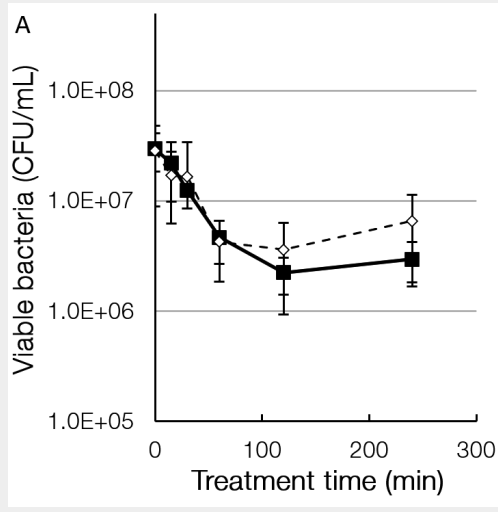


Figure 2: Comparison of the effect of 4 h exposure of XZ.700 (12.5, 25 and 50 μg/mL), povidone-iodine (PVP-I) (0.35%), and gentamicin (1000 μg/mL) on biofilm viability in 24 h (white bars) and 48 h (black bars)-old MRSA biofilms; *Significant reduction in biofilm viability compared to no treatment control, p<0.05; MRSA: methicillin resistant Staphylococcus aureus.



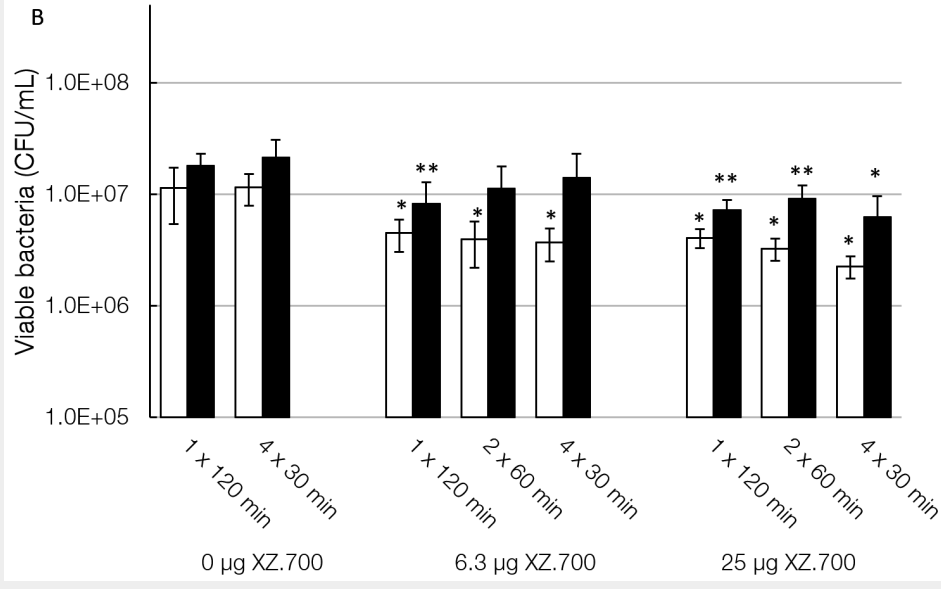


Figure 3: Panel A: Comparison of the effect of exposure times to XZ.700 (25 µg/mL) on viability of 24 h-old (dashed line) and 48 h-old (solid line) MRSA biofilms; *Significant reduction in CFU/ml compared to control, $p<0.05$. Panel B: Comparison of the effect of a single hit, two hits and four hits of XZ.700 (25 µg/mL and 6.25 µg/mL) on viability of 24 h-old (white bars) and 48 h-old (black bars) MRSA biofilms; *Significant reduction in CFU/mL compared to respective single hit control (1 x 120 min) and four hit control (4 x 30 min), $p<0.05$; **Significant reduction in CFU/mL compared to four hit control (4 x 30 min), $p<0.05$; MRSA: methicillin resistant Staphylococcus aureus; CFU: colony forming units.

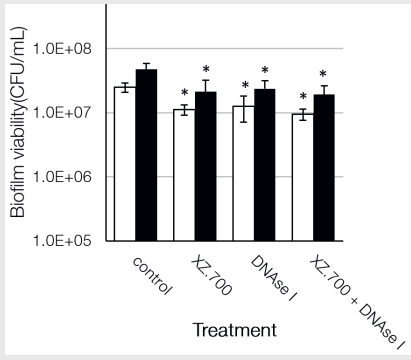


Figure 4: Comparison of the effect of 4 h exposure to XZ.700 (25 µg/mL), DNase I (50 U/mL) and both combined, on viability in 24 h-old (white bars) and 48 h-old (black bars) MRSA biofilms; *Significant reduction in biofilm viability compared to respective no-treatment controls, p<0.05; MRSA: methicillin resistant Staphylococcus aureus.

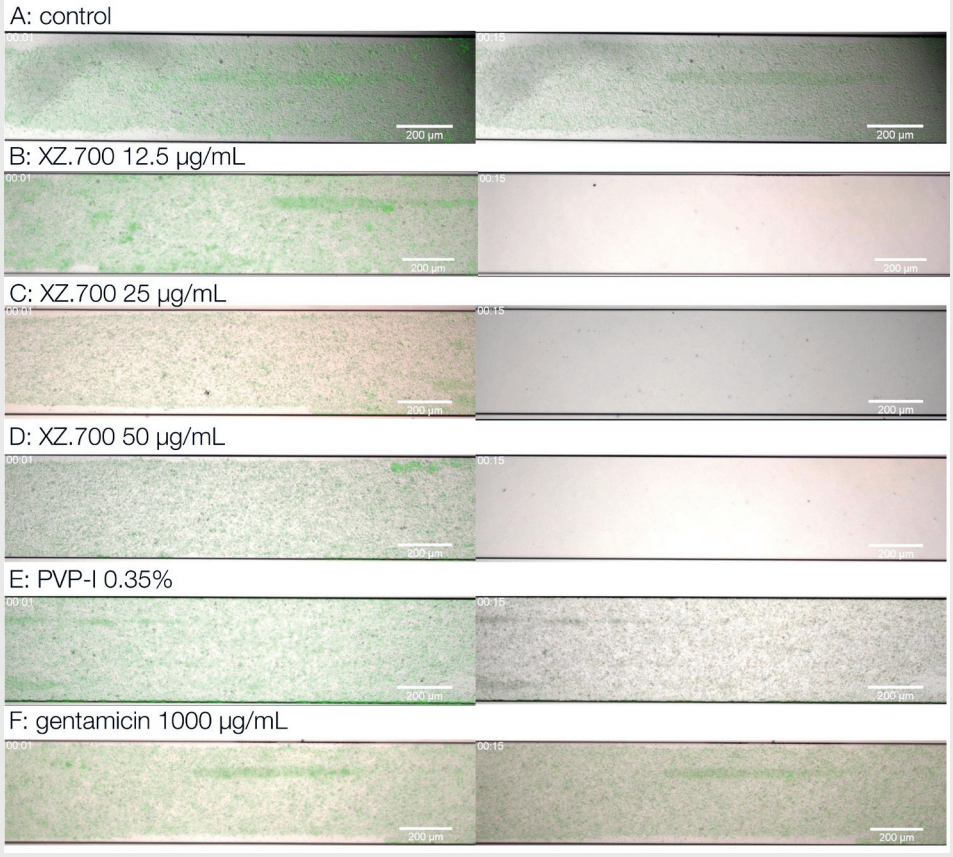


Figure 5: Time lapse microscopic images of the effect of different treatments on 16 h-old MRSA* biofilms cultured under flow conditions. Images obtained 1 min (left column) and 15 min (right column) after start of flow with A: control medium, B: XZ.700 12.5 µg/mL, C: XZ.700 25 µg/mL, D: XZ.700 50 µg/mL, E: povidone-iodine (PVP-I) 0.35%, F: gentamicin 1000 µg/mL. Green fluorescent protein (GFP) fluorescence is shown in green, propidium iodine (PI) fluorescence (indicative for cell death) is shown in red. The size bar represents 200 µm. *MRSA: methicillin resistant Staphylococcus aureus.

Comparison with povidone-iodine and gentamicin: After biofilm development for 24 and 48 h, the discs were immersed in serially diluted concentrations of XZ.700 (12.5-50 µg/mL) PVP-I (0.35%), gentamicin (1000 µg/mL), and a control, for 4 h. For 24 h-old biofilms, all three XZ.700 concentrations, PVP-I and gentamicin showed a significant reduction in viability, and PVP-I and gentamicin showed a higher reduction in viability than XZ.700 (95-99% versus 80-90%). For 48 h-old biofilms, all XZ.700 concentrations, PVP-I, and gentamicin showed a significant reduction in biofilm viability (Figure 2).

Effect of different exposure times and single, double, and quadruple hits: After biofilm development for 24 and 48 h, the discs were immersed in the most effective concentration of XZ.700 (25 µg/mL) for 0 (control), 15, 30, 60, 120 and 240 min. Maximum biofilm reduction was achieved after 60 min exposure and did not increase with increasing exposure times, achieving a significant reduction in viability for both 24 h and 48 h old biofilms (Figure 3A). After biofilm development for 24 and 48 h, the titanium discs were immersed in the most effective concentration of XZ.700 (25 µg/mL) for either 120 min, 2x 60 min or 4x 30 min, and this was also performed with 25% of the concentration for comparison purposes, and with two controls (1x 120 min and 4x 30 min of PBS). For multiple hits (2x 60 and 4x 30 min) the medium was directly exchanged. Double or quadruple hits did not show significantly more biofilm viability reduction than single hit treatment (Figure 3B).

Effect of DNAse I: After biofilm development for 24 and 48 h, the biofilm containing titanium discs were immersed in the most effective concentration of XZ.700 (25 µg/mL), DNAse I (50 U/mL; Sigma-Aldrich, St. Louis, MO, USA) with addition of 10 mM $MgCl_2$, and the combination of the two. A no-treatment control (PBS + 0.1% BSA + 10 mM $MgCl_2$) was used as a reference. XZ.700 achieved a similar reduction in viability compared to DNAse I and compared to the combined treatment methods (Figure 4).

Effect of XZ.700 on MRSA biofilms in a flow model

As shown in the supplementary videos (available at the *Biofouling* website or on request) and in Figure 5, in the Bioflux model, treatment with XZ.700 (12.5, 25 and 50 µg/mL; S2, S3, S4 respectively) achieved a rapid decrease in GFP activity and visible biofilm mass, i.e. within 10 min after exposure of the biofilm to XZ.700, GFP fluorescence disappeared, a slight peak in red fluorescence was seen, and all macroscopic biofilm was gone. The control (S1) showed an increase in GFP fluorescence over the course of 4 h after a small decrease in the first minute. The biofilms exposed to PVP-I (S5) and gentamicin (S6) showed the most pronounced decrease in GFP fluorescence in the first 30 min, after which the PVP-I-exposed biofilm showed almost no GFP activity, and the gentamicin-exposed biofilm showed some residual fluorescence. For both PVP-I and gentamicin-treated biofilms, biomass remained visible over the course of the experiment, in contrast to the XZ.700 treated biofilms.

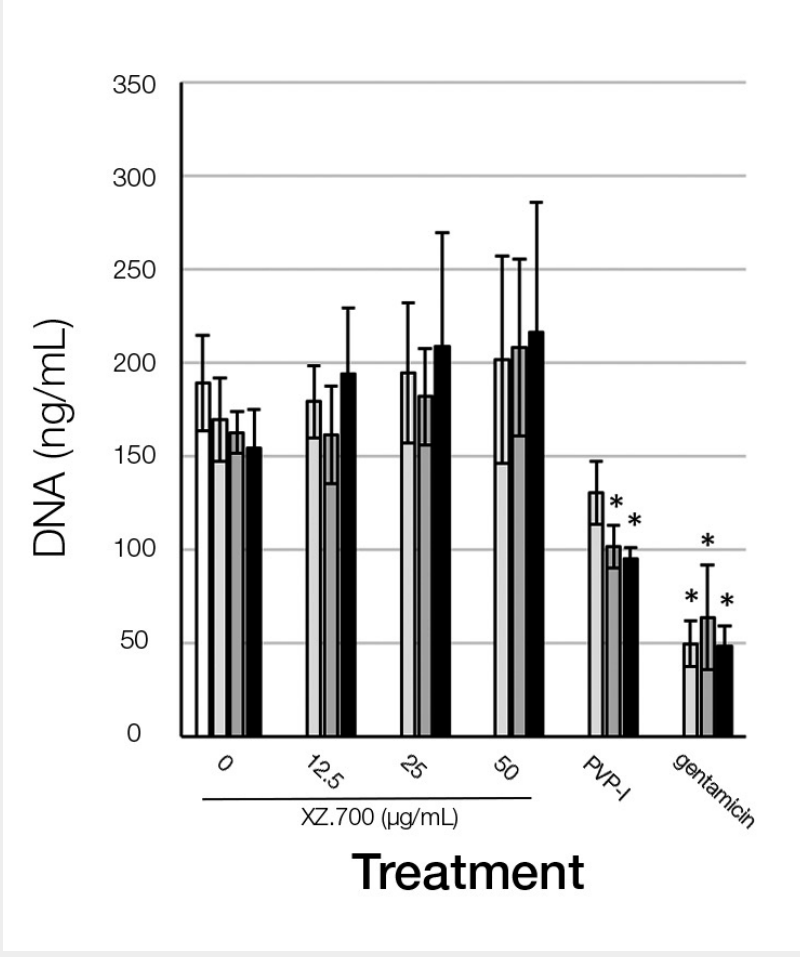


Figure 6: Proliferation of osteocyte-like cells (as amount of DNA), after 48 h exposure to 50% α-MEM and 50% MRSA biofilm supernatant, and a control (white bar; 100% α-MEM). The supernatants used were PBS + BSA (control), XZ.700 (12.5, 25 and 50 μg/mL), PVP-I (0.35%), and gentamicin (1000 μg/mL) in three different groups: without biofilm exposure (light grey bars), supernatant obtained after treatment of 24 h-old MRSA biofilm (dark grey bars), and supernatant obtained after treatment of 48 h-old MRSA biofilm (black bars); *: significantly lower than PBS + BSA and XZ.700 12.5, 25 and 50 μg/mL within own group; α-MEM: Minimum Essential Medium Alpha modification; MRSA: methicillin resistant Staphylococcus aureus; PBS: phosphate buffered saline; BSA: bovine serum albumin; PVP-I: povidone-iodine.

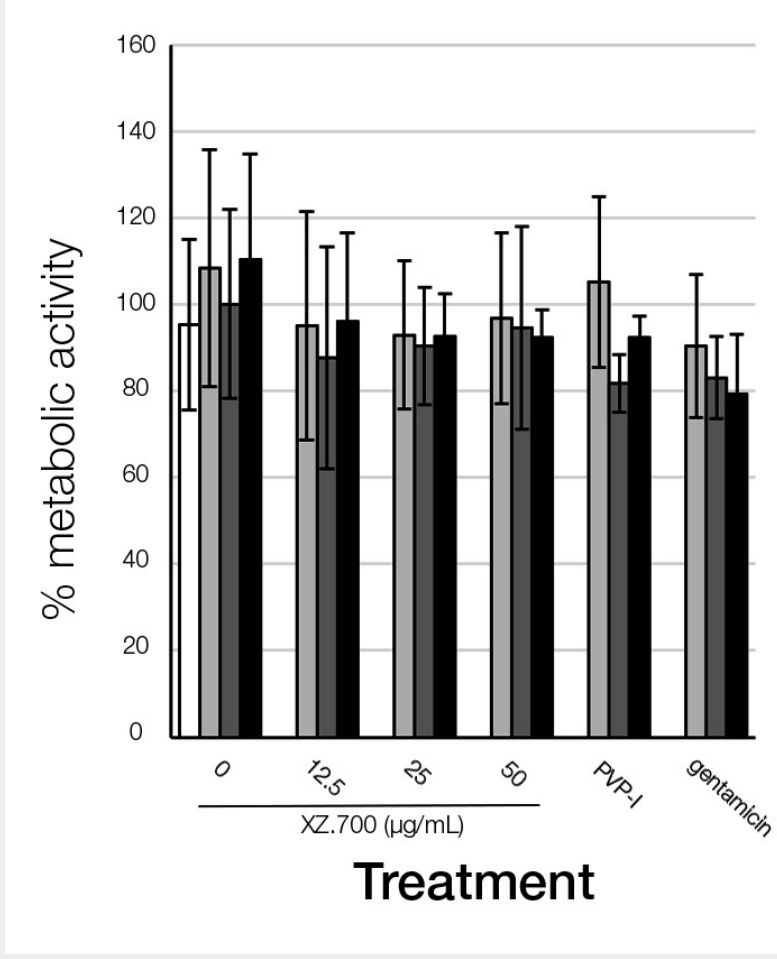


Figure 7: Metabolic activity of osteocyte-like cells, measured in percentage metabolized AlamarBlue, after 48 h exposure to 9% AlamarBlue, 45.5% α-MEM and 45.5% supernatant, and a control (white bar; 9% AlamarBlue, 91% α-MEM). The supernatants used were PBS + BSA (control), XZ.700 (12.5, 25 and 50 µg/mL), PVP-I (0.35%), and gentamicin (1000 µg/mL) in three different groups: without biofilm exposure (light grey bars), supernatant obtained after treatment of 24 h-old MRSA biofilm (dark grey bars), and supernatant obtained after treatment of 48 h-old MRSA biofilm (black bars); α-MEM: Minimum Essential Medium Alpha modification; MRSA: methicillin resistant Staphylococcus aureus; PBS: phosphate buffered saline; BSA: bovine serum albumin; PVP-I: povidone-iodine.

Cytotoxicity of XZ.700 supernatants on human bone cells

To study possible cytotoxic effects of XZ.700-induced biofilm lysates on human bone cell viability, cell cultures were exposed to supernatants obtained after biofilm exposure to XZ.700, PVP-I, and gentamicin.

After being exposed to the supernatants of XZ.700-treated 24 h-old biofilms (SN 24h) and 48 h-old biofilms (SN 48h), osteocyte-like cells showed a similar amount of DNA in comparison with untreated controls. Exposure to PVP-I (0.35%) and gentamicin (1000 µg/mL) derived lysates resulted in amounts of DNA that were significantly less (37-69%) compared to untreated controls (Figure 6).
Using the AlamarBlue assay, exposure to all different supernatants resulted in similar, normal cell metabolism for osteocyte-like cells (all results were between 79 and 112% compared to positive controls) (Figure 7).

Discussion

In this *in vitro* study, the new chimeric endolysin XZ.700 was effective in reducing the viability of 24 h-old and 48 h-old MRSA biofilms grown on titanium discs in a static model. In a flow model, a fast decrease in GFP fluorescence and visible biofilm mass was observed. The standard of care treatments, PVP-I and gentamicin, were used for comparison and showed a larger reduction in viability for 24 h-old biofilms in the static model, but appeared much less effective in the flow model. Furthermore, XZ.700 derived biofilm lysates showed no significant effect on metabolism and proliferation of human osteocyte-like cells, whereas PVP-I and gentamicin-derived biofilm lysates had a large inhibitory effect on cell proliferation.
XZ.700 was tested on MRSA biofilms using a static model as well as a flow biofilm model. Generally, in the static biofilm model with titanium discs, a significant reduction in viability of 80-90% (approximately 1 log) was achieved. In terms of bacterial viability count reduction, in the 24 h-old biofilm groups, PVP-I (0.35%) and high local concentrations of gentamicin (1000 µg/mL) performed better. The 48 h-old biofilm showed more treatment resistance for gentamicin, which is in line with known increased biofilm resistance to antibiotics[131]. Interestingly, this increase in resistance was not observed for XZ.700, which, like PVP-I, showed comparable reduction in biofilm viability compared to 24 h-old biofilms.

The flow biofilm model showed a rapid removal of MRSA biofilm after exposure to XZ.700, whereas PVP-I and gentamicin exposure showed decreased GFP fluorescence but no biofilm mass removal. This might be explained by the fact that in the Bioflux model, there is a continuous supply of fresh compounds and removal of cell debris that might inhibit the activity of XZ.700, representing *in vivo* conditions more closely[132].

In the static model, titanium was used for biofilm adherence, while in the Bioflux, for technical reasons, glass was used. Surfaces could affect the effectiveness of treatment.

A study that compared biofilms formed on plastic and titanium found comparable bacterial biofilm growth for the two materials, but slower recovery after gentamicin exposure for titanium compared with plastic[133]. It should also be noted that biofilms in the Bioflux are 16 h-old biofilms, compared to 24 h-old and 48 h-old biofilms in the static model.

Another factor to be considered in the differences between static models and the clinical situation, is the large extent of biofilm formation in the static model. As we used discs with a surface of approximately 150 mm^2, a conservative estimate of the extend of biofilm formation results in at least 10^5 CFU/mm^2. In contrast, studies that provide information on biofilm formation (CFU/mm^2) on actual arthroplasty components described numbers of around 10^1 CFU/mm^2 [134], and when determining these numbers indirectly they are around 10^0-10^2 [135,136]. This illustrates that the clinical situation is different from the static *in vitro* model: biofilms probably grow slower, impeded by the immune system, or more bacteria may die in the process, explaining the low number of viable bacteria in biofilms. More dead bacteria in the biofilm might result in decreased penetration of antimicrobial agents into the lower layers of the biofilm. Flow models may be a better representation of the clinical situation, mimicking the physiological flow of synovial fluid in joints, i.e., removing debris and constantly supplying nutrients, but *in vivo* studies are even more essential.

Interestingly, higher endolysin concentrations and longer exposure showed a trend in less efficacy in the static model. Two possible explanations can be offered: high concentrations might evoke competitive inhibition between binding and cutting sites of the endolysin through occupation of the bacterial surface, and longer exposure to the agent might provide new nutrients (of killed microorganisms) to still living bacteria and thus initiate regrowth. In the flow model, the highest concentrations were not tested, but regrowth was not seen after XZ.700 treatment. This is not unexpected, as cell debris (including nutrients) are flushed away during flow.

It was hypothesized that the extracellular matrix of the biofilm could inhibit activity of XZ.700, and DNase I treatment to disperse biofilm matrix would then enhance the effectiveness of XZ.700, as has been described for several antiseptic agents[137]. However, as no synergistic effect between DNase I and XZ.700 was found, it may be concluded that extracellular DNA (and associated biofilm matrix components) does not limit penetration or activity of XZ.700 in biofilms *in vitro*.

The endolysin XZ.700 and the obtained supernatant did not significantly affect osteocyte-like cells *in vitro*, even after 48 h of exposure, including bacterial lysis products after biofilm treatment (supernatants).

PVP-I and gentamicin showed significantly lower yields of DNA for osteocyte-like cells. PVP-I is known to be cytotoxic, and a recent study described a safe threshold of 80 ng/mL[138], which is 2000 times less than the concentration of 0.35% that is used in the

clinical setting (and used in this study), based on another study[114]. To test the antimicrobial effect, Zhao *et al.* used 0.5% PVP-I for bone matrix sterilization, and found 100% reduction after 24 h of immersion in PVP-I[138].

Gentamicin is known to affect proliferation of bone cells *in vitro*: one study found a decrease in total DNA yield for high concentrations of gentamicin (>700 µg/mL)[139], and another study found similar effects for another aminoglycoside, tobramycin[140]. In this study, the gentamicin-treated biofilm supernatants were diluted, resulting in a gentamicin concentration of 450 µg/mL.

For the AlamarBlue-based metabolic activity assays, cells were exposed to the treatment supernatants for 48 h. This *in vitro* experiment might be more extreme than the *in vivo* situation, where fluids are constantly refreshed, and (toxic) waste products are removed by the host. To the knowledge of the authors, this is the first study to investigate the effect of treatment supernatants after endolysin therapy on human cells. Our data indicates that XZ.700 does not have a measurable effect on proliferation (DNA content) of osteocyte-like cells, in contrast to the standard of care, PVP-I and gentamycin. Both PVP-I and gentamycin show an inhibitory effect on osteocyte-like cells. The observation that this inhibitory effect was not apparent in the metabolic activity (AlamarBlue) can be explained by a compensatory mechanism resulting in increased metabolic activity in stressed cells.

When comparing this study to others, other *in vitro* studies have shown similar or higher reduction in *S. aureus* biofilm viability in static models for different endolysins (LysK[118,119], LysCSA13[120], MR-10[121], CF-301[122]), indicating that several endolysins have shown a promising effect on biofilm-associated infections. However, endolysin therapy is still in its early stages, and although other endolysins performed well in static models, only one other study used a flow model (Biostream), achieving 80% reduction in staining[118]. Furthermore, to the authors' knowledge, a comparison with current standard of care local treatment agents, such as PVP-I and gentamicin, has not been previously described.

Conclusion

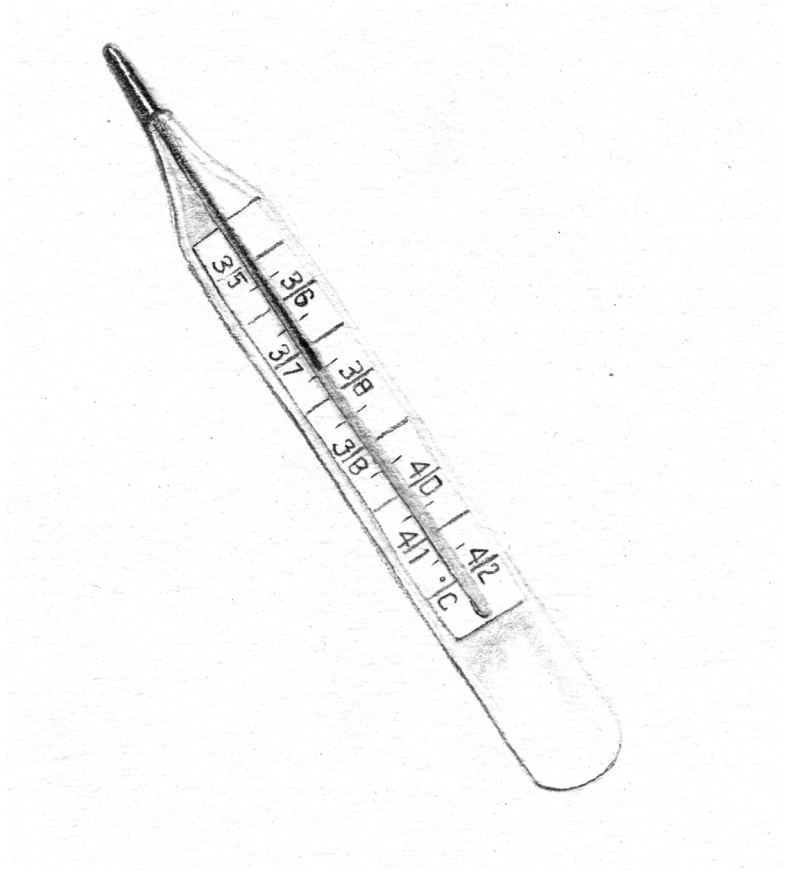
This study demonstrated the efficacy of endolysin XZ.700 on 24 h-old and 48-h old MRSA biofilms on titanium in a static model, with a reduction for MRSA biofilms of 80-90%. On 16 h-old MRSA biofilms on glass in a flow model, which is a better representation of clinical conditions, XZ.700 treatment resulted in fast killing of bacteria in the biofilm and removal of all biomass. Also, XZ.700, combined with bacterial debris components, showed no adverse effect on bone cells *in vitro*, unlike commonly used therapeutics such as PVP-I and gentamicin.

After this first *in vitro* study, XZ.700 seems a promising agent against (methicillin resistant) *S. aureus* on orthopedic material. Further *in vitro* evaluation and subsequent *in vivo* testing should be performed to determine successful application as treatment in orthopedic implant-related infections.

TREATMENT
OF PERIPROSTHETIC JOINT INFECTIONS

CHAPTER 7

Treatment of acute periprosthetic infections with prosthesis retention: review of current concepts



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CHAPTER 7

Treatment of acute periprosthetic infections with prosthesis retention: review of current concepts

Abstract

Periprosthetic joint infection (PJI) is a devastating complication after total joint arthroplasty, occurring in approximately 1-2% of all cases. With growing populations and increasing age, PJI will have a growing effect on health care costs. Many risk factors have been identified that increase the risk of developing PJI, including obesity, immune system deficiencies, malignancy, previous surgery of the same joint and longer operating time. Acute PJI occurs either postoperatively (4 weeks to 3 months after initial arthroplasty, depending on the classification system), or via hematogenous spreading after a period in which the prosthesis had functioned properly.

Diagnosis and the choice of treatment are the cornerstones to success. Although different definitions for PJI have been used in the past, most are more or less similar and include the presence of a sinus tract, blood infection values, synovial white blood cell count, signs of infection on histopathological analysis and one or more positive culture results. Debridement, antibiotics, irrigation and implant retention (DAIR) is the primary treatment for acute PJI, and should be performed as soon as possible after the development of symptoms. Success rates differ, but most studies report success rates of around 60-80%. Whether single or multiple debridement procedures are more successful remains unclear. The use of local antibiotics in addition to the administration of systemic antibiotic agents is also subject to debate, and its pros and cons should be carefully considered. Systemic treatment, based on culture results, is of importance for all PJI treatments. Additionally, rifampin should be given in staphylococcal PJI, unless all foreign material is removed.

The most important factors contributing to treatment failure are longer duration of symptoms, a longer time after initial arthroplasty, the need for more debridement procedures, the retention of exchangeable components, and PJI caused by *Staphylococcus* (*aureus* or coagulase negative).

If DAIR treatment is unsuccessful, the following treatment option should be based on the patient health status and his or her expectations. For the best functional outcome, one- or two-stage revision should be performed after DAIR failure. In conclusion, DAIR is the obvious choice for treatment of acute PJI, with good success rates in selected patients.

Introduction: etiology and pathogenesis

With an average infection rate of approximately 1-2%, periprosthetic joint infection (PJI) is a relatively frequent and devastating complication after performing joint arthroplasty[8,33]. It is especially debilitating for patients, as it requires prolonged hospitalization and often multiple surgical procedures. Besides the clinical impact of PJI, there is a high

economic impact with tremendously increased health care costs[104]. With a rising population and overall increasing age, the number of total hip arthroplasties performed are expected to increase significantly thereby having a growing effect on the number of PJI and, subsequently, on overall health care costs[141].
Most PJI are caused by intraoperative contamination and cause either early or delayed infection[33]. Hematogenous seeding is less common, and is most often seen years after the initial arthroplasty[8,14]. Although these types of infection have a different pathogenesis, both early postoperative and hematogenous infection usually have an acute onset and, therefore, both attribute to 'acute infection', based on similar symptoms and treatment options[36]. Chronic late infections are usually caused by less virulent microorganisms, and although these are also thought to occur from intraoperative contamination, symptoms develop very slowly. Therefore, patient complaints are often similar to those seen in aseptic arthroplasty loosening[8,24].
Although recent guidelines published by Osmon *et al.*[8] have provided some directive, classification of acute PJI remains difficult in borderline cases. For early postoperative PJI, the period after initial arthroplasty is reported, in literature, as being between 0-4 weeks[14] and 0-3 months[33]. For acute hematogenous infections, the (vague) definition encompasses acute symptoms in 'a previously well-functioning prosthesis', which can occur at any time postoperatively[8,14,142].
Microorganisms causing PJI are mainly *Staphylococcus aureus* and coagulase negative *Staphylococcus*, accounting for up to half or even three quarters of the infections[143,144]. Other microorganisms responsible include *Streptococcus* species, *Enterococcus* species, and gram negative bacteria[143,144]. The microbiological profile for acute versus chronic PJI is reported by only a limited number of authors, and shows that acute PJI is more often caused by *S. aureus* and *Streptococcus* species[14,145–147]. In comparison, chronic infections are more often caused by coagulase negative *Staphylococci* and *Propionibacterium acnes*[14,145–147].
In this review we will focus on acute PJI, both early postoperative as well as acute hematogenous PJI, after an initial symptom free period in which the arthroplasty functioned properly. First, we will clarify the definition of these infections. Which diagnostic tools can be used? Which risk factors are associated with developing PJI? Which microorganisms are a predominant cause of acute PJI? What kind of treatment options exist and what is the outcome of each of these treatment options? Finally, we will discuss the risk factors associated with failure of these treatments.

Definition of a periprosthetic joint infection

Several definitions of PJI have been used in the past decades. The Workgroup of the Musculoskeletal Infection Society published a well restricted definition[17]. In their definition the diagnosis of PJI can be made if:

- there is a sinus tract communicating with the prosthesis; or

- a pathogen is isolated by culture from at least two separate tissue or fluid samples obtained from the affected prosthetic joint.

In patients presenting without such clear indications, four of the following six criteria have to be present to prove the presence of PJI:

- Elevated serum erythrocyte sedimentation rate (ESR) and serum C-reactive protein (CRP) concentration,
- Elevated synovial leukocyte count,
- Elevated synovial polymorphonuclear neutrophil percentage (PMN%),
- Presence of purulence in the affected joint,
- Isolation of a microorganism in one culture of periprosthetic tissue or fluid,
- More than five neutrophils per high-power field in five high-power fields observed from histological analysis of periprosthetic tissue at x400 magnification.

Other authors have described similar definitions, of which some are used more frequently, either directly or slightly adapted[14,15,148]. There are yet other studies which use a less well-contained definition, for example only mentioning the diagnosis ('staged revision for septic loosening')[104], or mentioning only that the diagnosis was made based on several laboratory values and culture results[149].

Definition of acute, late chronic and acute late PJI

Two classification systems are most often used to determine whether or not there is an acute, late chronic or acute late PJI. Tsukayama *et al.* suggested a system which divides the occurrence of infection into four groups: positive intraoperative cultures (at time of implantation of the prosthesis), early postoperative infection (<4 weeks), late chronic (>4 weeks, indolent onset), and acute hematogenous (acute onset)[14]. This system was adapted by Toms *et al.* to early postoperative (type I, acute, <6 weeks), chronic (type II, chronic, indolent onset) and acute hematogenous (type III, acute onset in a well-functioning prosthesis, secondary to hematogenous spread)[32]. The other commonly used classification, proposed by Zimmerli *et al.*, defines the PJI as early (occurring within 3 months postoperatively), delayed (3-24 months) and late (>24 months)[33]. Parvizi *et al.* also mentioned a period of 3 months after performing arthroplasty as the cutoff to determine whether the infection can be regarded as being acute or not[150]. However, they referred to an article only including patients undergoing aspiration within 6 weeks postoperatively[151].

Diagnosis

Classical cornerstones of PJI diagnosis are, as for any disease, a thorough patient interview and physical examination. This includes evaluation of the patient's history

and comorbidities, medication use, postoperative wound problems and duration of infectious symptoms[8].
In addition to this, different diagnostics, such as infection parameters in the patient's blood (ESR and CRP), preoperative joint aspiration results (cell count, cell differentiation and culture) and intraoperative tissue and fluid culture results are equally important in order to determine the diagnosis of a PJI[8,17].

Blood analysis
Blood leukocyte count is unable to differentiate between the absence or presence of PJI[33]. ESR and CRP have a more discriminating ability, and ESR higher than 30 mm/hour, and CRP higher than 10 mg/L are suggestive for the presence of PJI[17]. However, shortly after surgery (such as in early infections), these parameters generally remain elevated for a prolonged period (30-60 days)[17]. Thus, a single high value is difficult to interpret, and serial measurements are recommended to aid in making the PJI diagnosis[33]. Several other serum markers have been studied for this purpose, such as interleukin-6. Studies have shown promising results, with high sensitivity and very high specificity, but it has not yet been included in recently published guidelines[8,152,153].

Preoperative joint aspiration
When PJI is suspected, preoperative aspiration is recommended in almost all cases, the exceptions being when it will not change further choice of treatment (e.g. presence of a sinus tract), and when the diagnosis (including the causative microorganism) has already been established[8]. The synovial fluid should be sent for culture, cell count and differentiation, for the determination of the percentage polymorphonuclear leukocytes.
Gram staining has a limited role in PJI diagnosis according to most authors[154–157]. Despite the fact that its specificity and positive predictive value are high, false positive results have also been mentioned. Furthermore, with a sensitivity of 20%, many PJI are missed[154–157].
Recent studies have focused on two new synovial fluid diagnostics including synovial CRP levels[158,159] and the use of leukocyte esterase strips (also used to diagnose urinary tract infections)[150,151,160]. These diagnostics appear to be promising in the diagnosis of PJI, but are not yet widespread.

Intraoperative samples
For the definitive diagnosis of PJI, multiple intraoperative samples should be obtained. It is recommended that between 4 to 6 samples should be sent for bacterial culturing[8]. The incubation period should be at least 7 days, but preferably 14 days[161]. The samples should be tissue samples or samples obtained from dislodging the bacterial biofilm from the prosthetic parts[8]. For dislodging, sonication is the preferred method[16]. Scraping the biofilm from the foreign material has a lower yield of microorganisms[162]. A relatively new but promising method is the use of dithiothreitol (DTT), an agent that has the ability to dislodge bacteria while also keeping them alive[163]. In addition to the culture samples, it is recommended that at least one sample is sent for histopathological determination of acute inflammation[8]. For a positive result, the average presence

of 1 or more neutrophil polymorphs per high power field in at least 10 high power fields is required[164].

Risk factors for (acute) PJI

Considering the substantial incidence of PJI it is important to recognize certain risk factors associated with the development of such an infection (risk factors associated with DAIR treatment failure will be discussed further on in this review).
Chen *et al.* performed a meta-analysis regarding risk factors for total knee arthroplasties[165]. Patient related factors that increase PJI risk include high body mass index (>30), diabetes mellitus, hypertension, steroid use and rheumatoid arthritis. Everhart *et al.* support these risk factors and found that revision surgery, tobacco abuse, MRSA colonization and infection and (a history of) bone cancer also play an essential role in PJI development[166]. They claim, however, that super obesity (i.e., A BMI >50) is a critical risk factor. Choong *et al.* found that there is a direct correlation between a BMI ≥ 30 and an increased risk of infection[148]. This correlation also exists if there are more than 2 co-morbidities present (cardiovascular, respiratory, renal, endocrine, gastrointestinal, neurovascular, vascular, oncological, hematological, urological, rheumatological, psychiatric, anticoagulation status, smoking status, height, weight, pre- and postoperative hemoglobin).
According to Liabaud *et al.* there is a significant, linear correlation between BMI and operating time[167], which is in line with Willis-Owens' results, claiming that "prolonged operating time and male gender are associated with an increased incidence of infection"[168]. Luessenhop *et al.* also found that a patient diagnosed with rheumatoid arthritis (and subsequent use of steroids) was at a greater risk for developing PJI[169].
Berbari *et al.* add that a patient with a system surgical patient risk index score of 1 or 2, the presence of a malignancy, and a history of joint arthroplasty are also risk factors[170].

Treatment

For acute infections with a stable implant and adequate soft tissue mass, the latest guidelines recommend implant retention treatment (also referred to as DAIR: debridement, antibiotics, irrigation and implant retention) for PJI occurring within 30 days after arthroplasty, or with less than 3 weeks of symptoms[8]. Osmon *et al.* noticed that DAIR may be used in patients who do not meet these criteria, but state that worse results can then be expected[8].
When patients do not meet the criteria to undergo DAIR treatment, revision surgery is the preferred treatment, either in one-stage (when tissue quality and microorganism susceptibility allow for direct exchange) or in multiple stages. Mere medical treatment should be reserved for patients in whom surgery is not the most preferred option or when it is medically irresponsible. Resection arthroplasty (without reimplantation),

arthrodesis and amputation are options for difficult to treat and chronic PJI, and these treatment options only very rarely have a role in acute PJI cases[8,33].

DAIR

DAIR treatment is probably the most widely performed initial treatment option for acute PJI, although the exact data on the number of such procedures performed is yet unknown. When acute PJI is suspected (or confirmed by the previously mentioned criteria) a debridement procedure should be performed as soon as possible, meanwhile keeping in mind that patient health optimization should also be maintained. For example, it has been seen that factors such as hyperglycemia and malnutrition adversely affect outcome after total joint surgery[171,172].

The procedure includes acquiring multiple tissue samples, excessive debridement and removal of all infected (and/or necrotic) tissue, exchange of modular components (head and acetabular insert) and extensive irrigation[8,36]. Compared to arthroscopic washout, DAIR is associated with higher success rates: Byren *et al.* reported a success rate of 47%, versus 88% for open washout, with a hazard ratio of 5.4[173]. Retention of modular components is also associated with a higher failure risk. A recent study including hip and knee arthroplasties showed higher success rates for exchange of modular components: 59% for exchange versus 44% for retention (HR 1.54)[42]. Another study showed 53% success for exchange versus 0% success for retention of modular parts for infected knee arthroplasties[41].

Success rates of DAIR treatment in general also show a great variety. Most small studies report success in approximately 60-80% of the cases, but these are selected groups. When looking at cohorts with more than 100 patients (including both hip and knee PJI), success rates lie between 31% and 78% (Table 1)[36,42,149,173–178]. A recent meta-analysis found a combined success rate of 46% for DAIR with one debridement procedure (n=710), and 52% for multiple procedures (n=175)[179].

Author	Year	Cohort type	Selection	n	Hip	Knee	Other	Success (n)	Success rate	Mean follow-up (m)
Azzam[36]	2010	retrospective cohort	-	104	51	53	-	46	44 %	68
Odum[149]	2011	retrospective cohort	-	150	53	97	-	46	31 %	n.m.*
Byren[173]	2009	retrospective cohort	-	112	52	51	9	92	82 %	27
Lora Tamayo[42]	2012	retrospective cohort	*Staphylococcus aureus* PJI	345	146	195	4	199	55 %	n.m.
Cobo[174]	2011	prospective cohort	Early PJI (<30 days)	117	69	53	17	67	57 %	24
Buller[176]	2012	retrospective cohort	-	309	62	247	-	160	52 %	34
Koyonos[175]	2011	retrospective cohort	-	138	60	78	-	48	35 %	54
El Helou[177]	2010	prospective cohort compared to 2 retrospective cohorts	Staphylococcal PJI	101	40	61	-	69	68 %	12
Tornero[178]	2012	retrospective cohort	Staphylococcal PJI	106	39	67	-	81	76 %	46

Table 1: Characteristics of studies on DAIR treatment with over 100 patients; DAIR: debridement, antibiotics, irrigation and implant retention; PJI: periprosthetic joint infection; n.m.: not mentioned; *: minimum 2 years.

Single versus multiple debridement procedures

Different strategies regarding debridement surgery can be divided into either performing only one debridement, a single debridement with repeat surgery on indication, or a more aggressive repeated debridement strategy[179]. Traditionally, when only local antibiotic cement beads were used, especially popular in Europe, the strategy of multiple debridements was necessary. However, when using resorbable local antibiotic carriers or no local antibiotics, a single debridement might be a sufficient alternative. Although the authors do not specifically mention it in their publication, in the Zimmerli algorithm a single open debridement seems to be favored as well[33]. The advocates of a single surgery may state that irrigation and debridement lowers the bacterial count sufficiently, prevents further soft tissue damage and that systemic antibiotic treatment is capable of achieving further eradication. The advocates of multiple debridements, on the other hand, may state that the surgeon should create a joint cavity, which is as sterile as possible and that surgery should continue until intraoperative cultures show no more bacterial growth.

Two studies on combined groups of total hip and knee patients suggest that a repeat debridement on indication increases the infection eradication rate compared to a single debridement[36,38]. There are also two studies that show good results using the strategy of routine multiple debridements[39,40]. Unfortunately, to date, no comparative studies between different strategies are available and therefore no hard recommendations regarding which one to use can be made. For every strategy different studies are published with results ranging from poor to excellent (21 to 90% success rate)[39,44,179,180]. All of them are retrospective case-series, which are often quite heterogeneous regarding inclusion, exact treatment and outcomes.

Local antibiotic treatment

Carriers for local antibiotic release include antibiotic loaded bone cement (polymethylmethacrylate, PMMA), beads and dissolvable sponges[130]. The rationale for using local antibiotic treatment is to achieve a high local concentration of antibiotic agents, thereby killing the causative microorganism, without the side-effects of high systemic concentrations.

Beads are usually loaded with gentamicin, but vancomycin and tobramycin are alternatively used. The beads are most often fabricated in chains of 30 beads. Locally, concentrations of around 300 µg/mL are achieved, far above minimum inhibitory concentration (MIC) values for most microorganisms[43,130,181]. A disadvantage of antibiotic beads is the additional removal surgery that is necessary, and their capability of forming a foreign body on which a biofilm can develop, after the antibiotic release (10-14 days)[43]. Their use in DAIR treatment has been reported in a few studies, with relatively high success rates: Tsukayama *et al.* (n=20, success 75%)[14], Tintle *et al.* (n=9, 100% success)[182], Estes *et al.* (n=20, 90% success)[40], and Geurts *et al.* (n=89, 83% success)[183]. Kuiper *et al.* also mentioned a subgroup treated with beads, albeit with lower success rates (n=12, 33% success)[44].

Gentamicin loaded collagen sponges, which are dissolvable, do not need removal surgery. Due to the quick expansion of the collagen, when water is added, the release of

gentamicin is fast, resulting in a very high local antibiotic concentration in the first hours, up to 3800 µg/mL[130,184]. The addition of hydrophobic gentamicin salt (gentamicin crobefat) has shown a longer release pattern, resulting in high concentrations (approximately 1000 µg/mL) for the first 40 hours. Up to 3-5 sponges can be used in patients, without reaching toxic serum concentrations[185]. A disadvantage of gentamicin sponges might be prolonged and increased wound secretion[183]. The clinical success rate of antibiotic loaded sponges in DAIR treatment for hip PJI has only been reported in one retrospective study, with a success rate of 70%[115].
Local continuous irrigation with an antibiotic pump or catheter is another option for local delivery. Its main advantage is that the agent can be changed, as well as the fact that it drains the intra-articular fluid. However, the patient burden is very high[186]. Reported success rates vary from 18-85%[186–189].

Systemic antibiotic treatment

In general, to eradicate PJI, both surgical and medical treatments are necessary[8,33]. Antibiotic treatment is recommended in all cases, and involves systemic administration of one or more antibiotic agents, based on the microorganism causing the PJI, for a period of at least three months[8]. Usually, in the first two to six weeks of treatment, antibiotics are administered intravenously, to achieve a better penetration of periprosthetic tissues, and thus a higher local concentration. Depending on the culture results, the intravenous administration might be switched to oral administration. This is a possibility if the microorganism is susceptible to an agent which reaches high tissue concentrations upon oral intake[8].
Culture results are the leading factor when choosing the appropriate antibiotic agent. Zimmerli *et al.* already described a medical treatment protocol in 2004, pointing out the best (combination of) antibiotic agents per causative organism[33]. This algorithm was adapted by recent guidelines, with the addition of several newer antibiotics, such as daptomycin for staphylococcal or enterococcal PJI[8]. No distinction is made between hip PJI and PJI in other joints in both studies[8,33].
All recommendations are based on the knowledge of the causative microorganism. What to do when PJI is suspected, but culture results are not yet known, is not mentioned in the guidelines. Only one study provides a treatment algorithm when PJI is suspected, but culture results are not (yet) known[35]. They advise the use of vancomycin for acute PJI caused by an unknown microorganism, and to switch to carbapenem if gram-negative bacteria are found. Another study, on culture negative PJI, mentioned the parenteral use of cefazolin in 69%, and vancomycin in 13% of culture negative cases, but this is of course a selected group, with many patients that were already treated with antibiotics prior to surgical treatment[190].
In almost all cases of DAIR, the addition of rifampin is useful. Rifampin is thought to penetrate the biofilm, and is recommended in all cases of staphylococcal PJI treated with DAIR[8,33]. Several studies describe the success rates of a regimen including rifampin[148,191–193], but only one prospective clinical study has been performed, which also observed higher success rates when rifampin was added to the antibiotic regimen[194].

Another, more recent study, compared a prospective rifampin group with a retrospective rifampin and a retrospective non-rifampin group[177]. They found higher success rates with the use of rifampin, but the groups were small, and included more knee rather than hip PJI. Despite the limited evidence, the use of additional rifampin is recommended in the most recent guidelines[8].

Risk factors for DAIR treatment failure

Several studies mention risk factors associated with a higher chance of treatment failure. PJI caused by a *Staphylococcus* infection is the most well documented and influential risk factor. Azzam *et al.* state that any staphylococcal infection, together with a high American Society of Anesthesiologists (ASA) score and intra-articular purulence, contributes to a substantial increase in failed treatments[36]. They claim that when "none or only one of these risk factors was present, a success rate of at least 67% was attainable". Vilchez *et al.*, Choi *et al.* and Deirmengian *et al.* all specifically mention *Staphylococcus aureus* as being much more virulent than other microorganisms (possibly due to their biofilm production) and having a significant, negative influence on treatment outcome[41,195,196]. Peel *et al.* specifically state MRSA infections as leading to a significant decrease in treatment success[197], whereas Kuiper *et al.* report that coagulase negative *Staphylococci* contribute to treatment failure[44]. Martinez-Pastor *et al.* claim that a fluoroquinolone susceptible microorganism leads to a better chance of treatment success[198]. This is in line with Jaen *et al.* who claim fluoroquinolone resistant bacteria to being risk factors for failure[199].

Another important risk factor appears to be the number of debridement procedures necessary, although the exact cut-off number varies. Vilchez *et al.* and Lora-Tamayo *et al.* state that the need for ≥ 2 debridements leads to an increased likelihood of failure[42,195], whereas Peel *et al.* set this number at > 4 (as previously mentioned)[197]. Specifically in knee PJI, lack of component exchange together with a S. aureus infection leads to much lower infection control rates, according to Choi *et al.*[41]. Lora-Tamayo *et al.* confirm the importance of component exchange, stating that this "is an independent predictor of (treatment) success"[42].

The duration of the presenting symptoms and the time after initial surgery are also important contributors to treatment success, or failure. Some studies state that treatment outcomes decline when the patients undergo a debridement a mere > 2 days after onset of symptoms[200], whereas other studies claim the cutoff is at > 7 days[44], 21 days[176] or even 28 days[115,201]. The time after index surgery showed an even greater scope, ranging from 15 days[178] to two years[202].

A patient's BMI and the presence of co-morbidities was only statistically significant in one study; Choong *et al.* state that a BMI > 30 and having > 2 co-morbidities are substantial risk factors[148]. Buller *et al.* and Byren *et al.* both describe that having a history of infection in the same joint as being associated with treatment failure[173,176]. Byren *et al.* also mention arthroscopic washout as a risk factor[173]. A higher ESR is a potential risk

factor[176], whereas a lower preoperative CRP, of ≤ 15mg/dL, leads to a better outcome[198]. Lora-Tamayo *et al.* confirm this, stating that the degree of complexity of the infection (polymicrobial, bacteremic, or presenting with high CRP levels) and immunosuppression were independent predictors of failure[42]. Kuiper *et al.* also describe rheumatoid arthritis as a significant risk factor[44].

Outcome after DAIR failure

As described above, DAIR treatment for PJI has a success rate of approximately 70%, which may even be higher in selected patients, e.g., those with a shorter duration of symptoms and without co-morbidities. The use of multiple debridement procedures remains up for discussion, as also previously described. However, when treatment definitely fails, another option must be sought to eradicate the infection.
The definition of DAIR treatment failure, just like the PJI definition, is not uniformly well described in the literature. Most studies do, however, consider DAIR as having failed when one or more of the following criteria are met after both surgical and medical treatment[39,115,148,203]:

- presence of local or systemic infectious symptoms;
- laboratory signs suggesting presence of PJI (e.g., CRP higher than normal laboratory values, usually 5 or 10 mg/L);
- the use of chronic suppressive antibiotics;
- signs of loosening on radiography;
- positive intraoperative culture result in a subsequent procedure;
- if the arthroplasty has been resected or replaced;
- or, death, resulting from PJI.

In the majority of the studies, after DAIR failure, most patients were treated with two-stage revision, but one-stage revision, resection arthroplasty without reimplantation and chronic suppression with antibiotics were described as well[15,39,115,148,203–205].
One-stage and two-stage revisions are preferred if function and eradication are important, but the patient must then endure one or more additional elaborate surgical procedures. For knee PJI, two studies suggest that two-stage procedures may have worse results if DAIR already has been attempted, but this has not yet been described for hip PJI[206,207]. If patient health status is poor, or his or her expectations are not high, an acceptable situation may be achieved with resection arthroplasty (Girdlestone arthroplasty) or the use of chronic suppressive antibiotics[8].
The choice of treatment after DAIR failure in the abovementioned cohorts was based on individual patient characteristics, if mentioned[115,148]. The recent IDSA (Infectious Diseases Society of America) guidelines advise individual judgment in all cases, but endorse the use of treatment algorithms when DAIR has failed, since it has been proven that their use increases treatment success[8]. Unfortunately, the current algorithms do not of-

fer help after the initial treatment choice[8,33,208,209]. If the symptoms remain and the tissue status progressively worsens, it may be possible to move down the algorithm thereby choosing an alternative treatment plan. However, in our opinion, it is much more important to choose a treatment method that fits the patient's and the doctor's expectations in regard to revalidation time, mobility of the patient and the chance of PJI eradication.

Discussion

This review is intended to provide a concise summary of all the currently available literature regarding acute periprosthetic joint infections. The various classifications, definitions and diagnostic tools used to make the diagnosis of PJI, as well as the use of DAIR were collected and analyzed in order to provide a series of solid treatment recommendations. The initial difficulty researchers and clinicians face is how to properly make the correct diagnosis. Patient interview and physical examination, together with a blood analysis, preoperative joint aspiration and intraoperative samples are of equal importance and must all be employed. Despite the fact that different authors use different criteria, in general all of these criteria and definitions are useful. The exact definition and cut-off of an acute infection remains unclear, however, due to the fact that some authors claim this be less than 4 weeks whereas other implement less than 6 weeks or even less than 3 months. Literature remains unclear whether a period of 3 months has worse outcome than 4 weeks.

Most of the risk factors for developing PJI are the same as the risk factors associated with DAIR treatment failure. A BMI of more than 30 kg/m^2, MRSA and the presence of multiple co-morbidities put all patients at an extra risk, for both infection development and subsequent treatment failure. However, there are some specific risk factors for failure of DAIR, like the number of debridements and the time between presenting symptoms and initial surgery. The sooner the DAIR is carried out, the better.

DAIR (with modular component exchange) remains the preferred initial treatment choice, before one- and two-stage revisions, mostly due to its less invasive character. Unfortunately DAIR has a lower success rate than one- and two-stage revision, respectively 70% versus higher than 90%[210]. There is no consensus regarding the optimal number of debridements necessary.

The use of local treatments such as beads, cement and sponges loaded with antibiotics appears to be promising, though only a handful of studies have been published, all of which analyzed a relatively small patient population.

Systemic antibiotic treatment is complementary to surgical treatment. The antibiotic used for PJI is based on the acquired culture results, potentially combined with rifampin in the case of a staphylococcal infection. However, too few studies have been published regarding the choice of antibiotics when the cultures are not yet known. Vancomycin (combined with cefazolin if necessary) appears to be a possible antibiotic option though a definite recommendation cannot be made. The duration of antibiotic administration is currently reported to be three months[8,33]. If the PJI cannot

be eradicated using minimally invasive approaches, one- and two-stage revisions are eventually the preferred treatment.
Despite many studies providing information about PJI, much evidence is missing. In order to provide stronger scientific evidence additional multicenter prospective and randomized trials must be carried out, using a single, uniformly agreed upon definition of APJI based upon equal criteria and diagnostic tools.

TREATMENT
OF PERIPROSTHETIC JOINT INFECTIONS

CHAPTER 8

Implantation of resorbable gentamicin loaded sponges in addition to irrigation and debridement in 34 patients with infection complicating total hip arthroplasty

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CHAPTER 8

Implantation of resorbable gentamicin loaded sponges in addition to irrigation and debridement in 34 patients with infection complicating total hip arthroplasty

Abstract

We evaluated a prosthesis-retaining treatment protocol for periprosthetic joint infection in patients presenting at a mean of 116 days (range 10-1216 days) after primary arthroplasty. Our regime involved irrigation and debridement followed by implantation of biodegradable gentamicin loaded sponges which do not require removal after implantation. Of 34 patients with a deep infection after total hip arthroplasty, twenty-five were treated successfully, with a mean follow-up of 35 months. There were no permanent complications. This success rate is comparable to earlier studies. Early initiation of treatment demonstrated a tendency for better results, and late chronic infections had a worse outcome. Because the sponges are degradable, a number of further surgical procedures were avoided.

Introduction

Deep intra-articular infection following total hip arthroplasty (THA) remains one of the most challenging problems facing orthopedic surgeons, occurring in around 1-2% of all patients[33,48,211,212]. Various treatment methods for periprosthetic joint infection (PJI) have been used, the most successful of which is the two-stage revision (success rate 86-96%[33,209,211,213–215]). Debridement and retention of the hip prosthesis is a less drastic method, being less debilitating for the patient. Success rates vary dramatically, ranging from 14% to 92%, with an average of around 70%[14,15,220,173,191,209,214,216–219]. Reported studies all used different debridement procedures, and most included less than twenty cases. Patients with favorable factors for outcome have tended to be selected for this procedure, such as short duration of symptoms and early onset of infection after primary surgery.
In our hospital the same treatment protocol is used for all patients with PJI of the hip, consisting of irrigation and debridement of the infected prosthesis and subsequent retention of the prosthesis combined with implantation of resorbable gentamicin-loaded sponges. This regimen is repeated up to three times if necessary, depending on symptoms and inflammatory markers. In addition, patients receive systemic antibiotics. Should the infection persist after three irrigation procedures, a two-stage revision procedure is performed.
Gentamicin-loaded sponges achieve a 1000-fold higher local concentration of gentamicin than systemic administration. Patients treated according to this method generally require one less surgical procedure compared to those treated with antibiotic beads, because removal surgery is not required, and the local dose of gentamicin released from sponges is much higher than from beads, resulting in a greater local antibiotic effect[130,181,185,221–223].

The goal of this study was to evaluate the above treatment method. Data were gathered on success rates and complications after treatment with resorbable antibiotic sponges, which was then compared to more invasive treatment regimens used in other studies. The data were analyzed to identify factors contributing to success.

Methods

Study population

To evaluate the protocol used, a retrospective study was carried out on the outcomes of a cohort of patients treated for periprosthetic joint infection (PJI) after total hip arthroplasty (THA) in the period from January 2004 until December 2009 (primary and revision THA, all indications for arthroplasty).
This study included patients who received a THA and were subsequently treated for PJI in our hospital (see definitions, Table 1), using a protocol involving irrigation, implantation of antibiotic sponges and subsequent intravenous antibiotic treatment. The treatment protocol was initiated in all cases suspected of deep infection, based on clinical symptoms, laboratory results and culture results. All cases treated according to this protocol were collected by searching the hospital's arthroplasty database. Patients were included when the first irrigation procedure was performed between January 2004 and December 2009.
PJI was suspected based on clinical symptoms, blood infection parameters, culture results, and clinical course, and retrospectively confirmed. Patients were excluded when infection criteria were not met (Table 1).

Outcomes

The primary outcome of this study was treatment success, defined as the absence of general and local infectious symptoms, and C-reactive protein (CRP) blood levels <10

Culture-positive infection	**Growth of the same microorganism in at least two culture specimens (preoperative joint aspiration or intraoperative specimen), or** **One positive culture result (either preoperative aspiration or intraoperative specimen) and one of:** - intracapsular purulence during debridement procedure; - acute inflammation on histopathologic examination of intraoperative specimen; - an actively draining sinus tract.
Culture-negative infection	**Negative culture results and two of:** - intracapsular purulence during debridement procedure; - acute inflammation on histopathologic examination of intraoperative specimen; - an actively draining sinus tract.

Table 1: Definition of periprosthetic joint infection (PJI)[15,148,191,219,224].

mg/L, without the need for suppressive antibiotic treatment or a removal procedure, at final follow-up. Patients who were treated successfully were compared to patients in whom treatment failed, to evaluate factors which may influence treatment outcome.

Definitions

The diagnosis of PJI is controversial, and previous publications have used differing definitions. In this study, the definition from Crockarell *et al.* (mainly based on Tsukayama *et al*.) was used, due to its accuracy and overlap with most of the definitions used in other studies (Table 1) [15,148,191,219,224].

Data collection

The following data were collected from the electronic patient file: patient sex; age; age at surgery; date of primary surgery; morbidity; duration and type of symptoms; type of infection (Table 2); time after primary surgery; preoperative and follow-up CRP blood levels; pre- and intraoperative culture results; presence of intracapsular purulence and or sinus tract; results of histopathologic examination; date and number of irrigation procedures; number of antibiotic sponges implanted; removal procedure executed; date of death or last contact; duration of antibiotic treatment.

	Infection type	Description	Criteria Used
I	Early postoperative	Symptoms less than four weeks after surgery	- Symptom duration < 4 weeks - Symptom onset < 4 weeks after THA
II	Late chronic	A gradual onset of symptoms with a duration of more than four weeks	- Symptom duration > 4 weeks - Gradual onset
III	Acute hematogenous	Acute onset in a previously well-functioning prosthesis	- Symptom duration < 4 weeks / acute onset - Symptom onset > 4 weeks after THA

Table 2: Classification of periprosthetic joint infection (PJI)[14,225–227]; THA: total hip arthroplasty.

Procedure (Figure 1)

The irrigation procedure was carried out according to the following protocol: when wound drainage was still present after six weeks after primary surgery, or if PJI was suspected, based on clinical symptoms such as fever, redness or pain, positive culture results or high infection parameters (CRP), and no loosening was seen on radiographs, an irrigation procedure was performed. During surgery, the prosthesis was exposed and swab cultures and tissue cultures were collected. After debridement the wound was extensively rinsed with a high-pressure device, using NaCl 0,9% solution. Five gentamicin-loaded sponges (Garacol®, gentamicin sulfate in equine collagen, 130 mg per sponge, EusaPharma, Oxford, UK,) were implanted, unless the patient's renal function was abnormal (indirectly estimated glomerular filtration rate (GFR) using the creatinine blood value). If this was the case, three or less sponges were implanted.
After the first irrigation and debridement procedure, intravenous vancomycin (Vanco-

mycin, 1000 milligrams twice daily, Xellia Pharmaceuticals ApS, Denmark) was initiated, when contraindications were excluded. The vancomycin treatment was adapted according to the intraoperative culture results, after consultation with a microbiologist. Forty-eight hours after starting treatment with vancomycin, oral or intravenous rifampicin (Rifadin, 600 mg twice daily, Sanofi Aventis, Netherlands) was added to the treatment, if the patient had no contraindications to rifampicin. This irrigation procedure was repeated up to three times if necessary, with two weeks between each procedure during which the intravenous antibiotic treatment continued. Hospital stay thus lasted between two and six weeks, depending on the number of irrigations. The decision to repeat the procedure

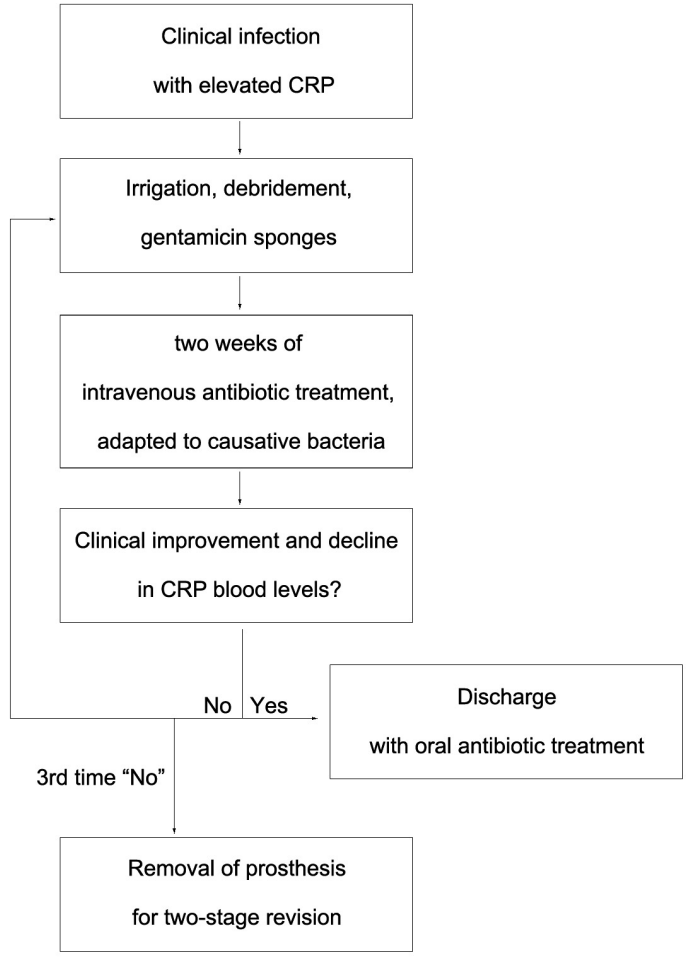


Figure 1: Protocol used for periprosthetic joint infection (PJI) treatment of total hip arthroplasty (THA); CRP: C-reactive protein.

was taken by the team of orthopedic surgeons, based on a lack of improvement in both clinical and CRP blood levels, within two weeks after the previous procedure.
After discharge, oral antibiotic treatment was continued for three months, with frequent evaluation of infection parameters. If the infection persisted after three irrigation procedures, the prosthesis was removed. Reimplantation surgery was performed a few months later, after elimination of the infection (two-stage revision) (Figure 1).

Statistical analysis

The Kaplan Meier method was used to estimate the success rate after at least two years of follow-up. The results of the treatment method were compared to results from previous studies. Data were analyzed with SPSS 16.0 (SPSS Inc. 2007, Illinois, USA). Chi-square tests, Fishers exact test for discrete data, and t-tests for continuous data were used in analyzing the data.

Included patients

During the period of January 2004 to December 2009, 45 patients were treated for suspected PJI of the hip, on a total of 2501 arthroplasties performed. Eleven cases were excluded: two patients had their primary arthroplasty in another hospital, eight patients did not meet the criteria for infection definition, and one patient underwent direct removal surgery because of radiographic loosening. The remaining 34 patients were included in the study.

Results

Twenty-five of the 34 patients were free of infectious symptoms and had CRP blood values <10 mg/L at follow-up. Using a survival analysis, we achieved a success rate of 70% (95% confidence interval 49-84%, see Figure 2). Treatment failure was seen in nine patients, of which eight occurred in the first six months of follow-up. All patients had a follow-up of at least two years, with a mean follow-up of 35 months (range 24-72 months). After being diagnosed with PJI, patients had a mean of 2.24 surgical irrigation procedures.
Of the nine patients with failure of treatment, seven had their prosthesis removed because of a persisting infection after the treatment protocol. Of these, four have had a revision THA, 3-6 months after the removal procedure, all of which are free of infection at present (8-52 months after revision surgery). One patient continued using suppressive antibiotics after the standard period of three months, and one patient had a CRP blood value of 24 mg/L and an isotope bone scan suspicious of low-grade infection after two years of follow-up. The intraoperative culture yielded group G *Streptococcus*. She felt no need for further treatment, as she had little pain and no further symptoms.
Of the 34 patients included, five patients died during follow-up due to causes unrelated to surgery or PJI, with mortality occurring 24-50 months after the irrigation procedure. Four of these cases experienced successful treatment. One patient with rheumatoid ar-

thritis had removal surgery and no further reimplantation, and died more than four years later as a result of a urinary tract infection.
During follow-up, no persistent complications of gentamicin use were reported. Of 34 patients followed, two had preoperative renal dysfunction, as a consequence of which fewer antibiotic sponges were implanted. Both patients were treated successfully. Four out of 34 patients developed high creatinine blood levels during treatment, as a result of which the number of gentamicin loaded sponges was decreased in subsequent irrigation procedures. All of these patients remained free of infection during follow-up, while creatinine blood levels all returned to preoperative levels.
A declining success rate was seen with longer periods since symptom onset, suggesting a better outcome for patients treated quickly (74% success when treated within a week, 73% for treatment starting after one week, 60% for two weeks and 0% when treatment was started after more than four weeks of symptoms). A delay of more than four weeks after symptom onset, although seen in only two cases, had a worse outcome than treatment within four weeks (74% versus 0%, p = 0.016) (Table 3).
Symptom onset at more than three months after the initial THA procedure was uncommon, occurring in only seven patients (18%), with a success rate of 57% (four out of seven patients), versus 78% (21 out of 27 patients) for early infections.

When using the previously mentioned, accepted classification system (definition: Table 2), a 100% failure rate was seen for patients with a late chronic infection (type II) (2/2),

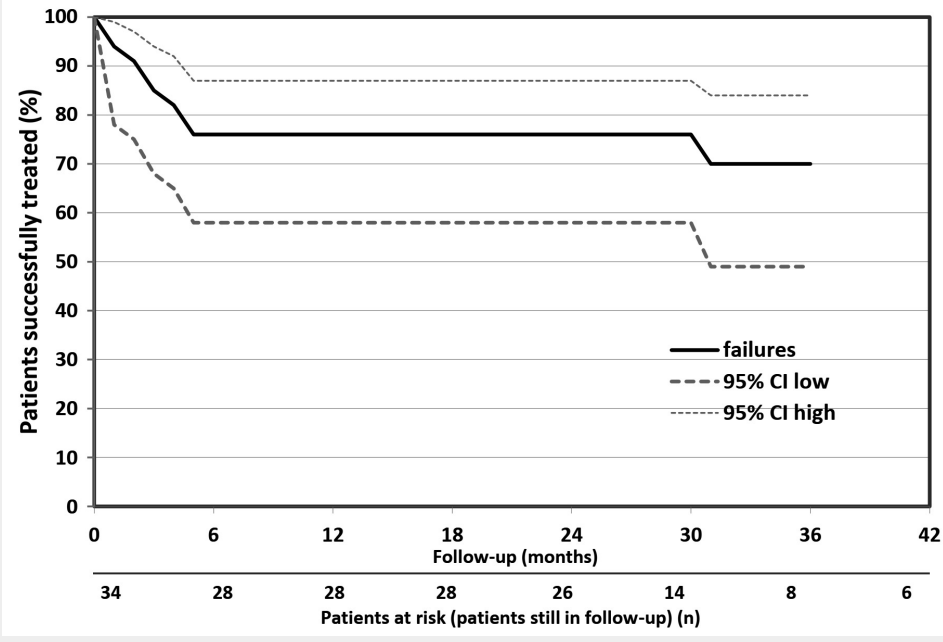


Figure 2: Percentage of patients free of infection after treatment with debridement and retention during follow-up (in months); CI: confidence interval.

	Total number of patients	*Success of treatment*	*Failure of treatment*	*p-value*
All	34	25 (73 %)	9 (27 %)	
Age (range) (years)	73 (56-86)	73 (56-86)	72 (63-80)	
Sex				
Male	12 (35%)	9 (75%)	3 (25%)	
Female	22 (65%)	16 (73%)	6 (27%)	
Follow-up (range) (months)	35 (24-72)	34 (24-72)	38 (25-52)	
Number of irrigation procedures				
1	6	4 (67%)	2	
2	14	11 (79%)	3	
3	14	10 (71%)	4	
Mean	*2.24*	*2.24*	*2.22*	
Start of treatment after onset of symptoms				
< 7 days	23	17 (74%)	6 (26%)	0.942
≥ 7 days	11	8 (73%)	3 (27%)	
< 2 weeks	29	22 (76%)	7 (24%)	0.458
≥ 2 weeks	5	3 (60%)	2 (40%)	
< 4 weeks	32	25 (74%)	7 (26%)	0.015*
≥ 4 weeks	2	0 (0%)	2 (100%)	
Early or late infection				
Early (< 90 days)	27	21 (78%)	6 (22%)	0.270
Late (≥ 90 days)	7	4 (57%)	3 (43%)	
Type of infection				
Acute postoperative (I)	26	20 (77%)	6 (23%)	
Late chronic (II)	2	0 (0%)	2 (100%)	
Acute hematogenous (III)	6	5 (83%)	1 (17%)	

Table 3: Success versus failure of treatment for periprosthetic hip infection in this study: patient and clinical characteristics; *: p-value <0.05.

whereas failure rates in early postoperative infections (I) and acute hematogenous infections (III) were 23% (6/21) and 17% (1/6) respectively.

The different bacteria found from intraoperative cultures are shown in Table 4. In all 34 cases at least one intraoperative sample yielded positive culture results.

In one case, multiple organisms were cultured: *Staphylococcus aureus* (one positive culture) and *Staphylococcus epidermidis* (two positive cultures). As purulence was found during surgery, infection criteria were met for both species. The patient remained free of symptoms after three procedures.

In five cases of treatment failure (56%), the number of irrigation procedures was less than three. In one case, the patient was admitted with coagulase negative *Staphylococcus* sepsis, which did not improve after the first debridement. Two days later, the prosthesis was removed. Four patients showed initial clinical improvement and a decline in CRP after one (one patient) or two procedures (three patients), and were discharged from the hospital.
Persistence of the infection was diagnosed a few months later in three cases. One patient seemed to be treated successfully until she complained of recurrent pain, and CRP blood levels were abnormal, after two years. Scintigraphy was suspicious for low-grade infection. No large differences in success rate were found between patient groups undergoing one, two or three irrigation procedures (67%, 79% and 71% respectively)

Bacteria	Number of patients	Success of treatment	Failure of treatment
Staphylococcus	24	17	7
aureus	15	12	3
MRSA	2	2	0
CNS (including *Staphylococcus epidermidis*)	7	3	4
Streptococcus spp.	4	3	1
Enterococcus faecalis	3	3	0
Other	4	3	1

Table 4: Success versus failure of treatment for periprosthetic joint infection of the hip; bacteria cultured (intraoperative samples); MRSA: methicillin resistant *Staphylococcus aureus*; CNS: coagulase-negative *Staphylococcus*.

Discussion

This retrospective study represents the first evaluation of a treatment protocol for PJI of the hip using gentamicin loaded sponges, showing a success rate of 70%, with a follow-up of more than two years, and a mean of 2.24 surgical irrigation procedures being performed. No patient selection was performed, except for radiographic loosening. Replacement of the head and insert was not part of the standard procedure, and could possibly have improved the results of our protocol.
Lower success rates were seen in patients with delayed treatment after symptom onset, with a significantly lower success rate in patients with chronic late infections (treated more than four weeks after the onset of symptoms, Table 2). Similarly, a higher treatment failure rate was seen when the infection occurred more than three months after the initial arthroplasty.
Treatment started more than a week after symptom onset was successful in 73% of the cases, dropping to 60% after two weeks and 0% after four weeks. This difference in outcome for patients with early treatment as opposed to late treatment might be

explained by the absence of a biofilm in early infection, as suggested in previous studies[48,211]. Furthermore, earlier treatment reduces the opportunity for bacteria to multiply, so the bacterial load is less.

Mortality

Five patients died during follow-up, of whom four were successfully treated, and one had removal surgery four years prior to death. None of these deaths was a consequence of THA or THA infection.

Causative agents

Most infections were caused by *Staphylococcus aureus* (17 out of 34 patients, 50%). Coagulase negative *Staphylococcus* (CNS) was responsible for seven cases of infection (21%). These rates are similar to those reported by Marculescu *et al.* (32% and 23% for *S. aureus* and CNS, respectively). However, they experienced a higher risk of treatment failure for *S. aureus*, as did Byren *et al.*, which differs from the success rates we found (70% and 43%)[173,217]. This might be explained by a difference in patient selection, the inclusion of other prosthetic joints than THA in these studies, by regional differences in *S. aureus* strains, or by our small study size.

Only 2 of 17 (12%) *Staphylococcus aureus* infections in the population we studied were attributable to MRSA (methicillin resistant *Staphylococcus aureus*). Other studies report similar MRSA rates: 11% (Sharma *et al.*), 19% (Byren *et al*.), 6% (Marculescu *et al.*)[144,173,217]. Although MRSA is reported to be more difficult to treat[173,224,225], the two cases in our study were both successfully cured of infection.

Three out of four streptococcal infections were cured (75%) in our group. A high cure rate for these infections is also seen in other studies[217,228].

Demographics

Male patients accounted for 34% of the patient population, which is comparable to the 1:2 male-female ratio in our general THA population. We have no reason to believe that a correlation exists between the patients excluded and infectious complications, i.e., that selection bias occurred.

Due to infection being a rare complication of total hip arthroplasty, the size of this study is small: 34 patients with affirmed infection in six years and 2501 THA procedures performed in the same period. We believe the lack of statistically significant findings can be attributed to the small study size.

Comparison to previous studies

When comparing our results to other studies, several differences are seen.

Giulieri *et al.* managed seven cases of PJI with success in eleven THA infections (64%). They selected patients according to a treatment algorithm, choosing debridement and retention for patients with an acute onset infection, with a stable implant, intact soft tissues and no additional problems[209].

Six out of 42 patients (14%) were successfully managed by Crockarell *et al.* No selec-

tion had taken place beforehand. They described a trend of difference in success rate between patients treated within a week after symptom onset and patients treated more than a week after onset of symptoms, which is comparable to our study[15].
Krasin *et al.* successfully treated five out of seven patients (71%) with an acute PJI (less than two weeks), with debridement, antibiotics, irrigation and implant retention[216].
The difference in outcome for patients with early treatment as opposed to late treatment has also been described by Marculescu *et al.* A two-year survival rate free of infection of 60%, in 99 cases of PJI, was found after debridement and retention of the prosthesis. The choice for this treatment option was made by the orthopedic surgeon individually in every case, so selection criteria are unknown[217].
Tsukayama *et al.* treated a selection of patients with debridement and retention with a success rate of 71% for early postoperative infections and 50% for acute hematogenous infections; an overall success rate of 68%. They did not manage late chronic infections with this regimen[14].
Eleven patients out of 14 (77%) were treated successfully for an infected THA by Trebse *et al*. Selection was made based on culture results, absence of a sinus tract, a stable implant and symptoms of infection lasting no longer than one year[220].

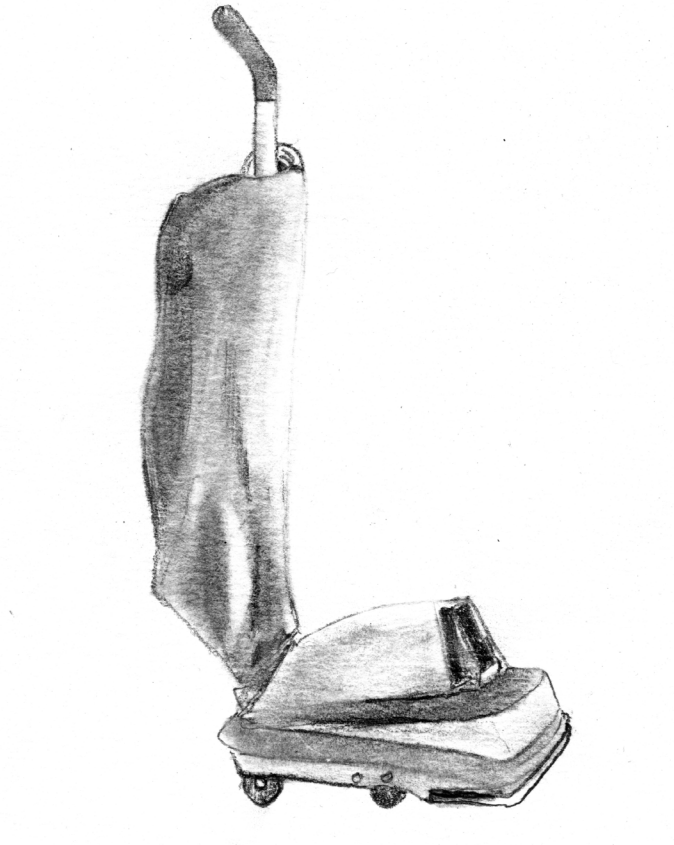
Evaluation

The irrigation procedure described above was applied to all patients treated in our hospital for PJI following THA, as we believe this method to be much less debilitating for patients compared to two-stage revision. One exception was made for a patient with preoperative radiographic loosening.
Our irrigation procedure was repeated up to three times if necessary. When blood values of CRP started to fall and the patient's clinical condition improved after the first or second procedure, a further procedure was not performed. In three cases of treatment failure, patients were discharged before undergoing three procedures because of such improvement, and therefore there is no guarantee of success.
With a mean of 2.24 irrigation procedures per successfully treated patient, 25 patients received a total of 56 procedures. The need for final surgical removal (e.g., if beads had been used) would have resulted in a 45% increase in the number of surgical procedures (81 instead of 56), with potentially increased costs and patient morbidity.
We believe that our results suggest favorable outcomes using gentamicin-loaded sponges, especially when treatment is initiated as soon as possible after symptom onset, and when the infection occurs within three months after initial surgery. When a patient has had symptoms for more than four weeks, it seems irrigation and debridement is unsuccessful, and a two-stage exchange revision may be a better option. The overall success rate of 70% is comparable to success rates for irrigation and debridement in previous studies.
More studies are necessary to determine the effectiveness of treatment with resorbable antibiotic materials, preferably randomized clinical trials with large sample sizes, comparing this treatment method to other more common methods, such as the implantation of beads. However, since infection rates are relatively low, achieving large sample sizes would involve a large, multicenter, trial.

TREATMENT
OF PERIPROSTHETIC JOINT INFECTIONS

CHAPTER 9

Prosthetic joint associated infections treated with DAIR (debridement, antibiotics, irrigation, retention) in the Netherlands: analysis of risk factors and local antibiotic carriers



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CHAPTER 9

Prosthetic joint associated infections treated with DAIR (debridement, antibiotics, irrigation, retention) in the Netherlands: analysis of risk factors and local antibiotic carriers

Abstract

For prosthetic joint-associated infection (PJI), a regimen of debridement, antibiotics, irrigation and implant retention (DAIR) is generally accepted for acute infections. Various risk factors associated with treatment success have been described. The use of local antibiotic carriers (beads and sponges) is relatively unknown. We retrospectively analyzed risk factors in a cohort of patients from three hospitals, treated with DAIR for PJI.
91 patients treated with DAIR for hip or knee PJI in three Dutch centers between 2004 and 2009 were retrospectively evaluated. The mean follow-up was 3 years. Treatment success was defined as absence of infection after 2 years, with retention of the prosthesis and without the use of suppressive antibiotics.
60 patients (66%) were free of infection at follow-up. Factors associated with treatment failure were: a history of rheumatoid arthritis, late infection (> 2 years after arthroplasty), ESR at presentation above 60 mm/h, and infection caused by coagulase-negative *Staphylococcus.* Symptom duration of less than 1 week was associated with treatment success. The use of gentamicin sponges was statistically significantly higher in the success group, and the use of beads was higher in the failure group in the univariate analysis, but these differences did not reach significance in the logistic regression analysis. Less surgical procedures were performed in the group treated with sponges than in the group treated with beads.
In the presence of rheumatoid arthritis, duration of symptoms of more than 1 week, ESR above 60 mm/h, late infection (> 2 years after arthroplasty), and coagulase-negative *Staphylococcus* PJI, the chances of successful DAIR treatment decrease, and other treatment methods should be considered.

Introduction

Periprosthetic joint infection (PJI) occurs in around 1–2% of primary total hip arthroplasties (THA) and total knee arthroplasties (TKA)[48,212,229]. Infected artificial joints are often unresponsive to antibiotic treatment, due to poor vascular supply and biofilm formation. Generally, PJI are classified in three groups, based on duration of symptoms and time after surgery: (I) early postoperative: symptoms less than 4 weeks after surgery; (II) late chronic: a gradual, indolent onset of symptoms; or (III) acute hematogenous: acute onset in a previously well-functioning prosthesis[14,32]. A similar classification describes early (3 months), delayed/low-grade (3–24 months), and late infection (> 24 months)[48].
Various risk factors have been described that are associated with occurrence of PJI, such as rheumatoid arthritis, diabetes mellitus, malignancy, obesity, and use of immunosuppressant drugs[36,42,148,230,231]. Revision surgery also increases the risk of PJI[173,230,231].

Factors that have been associated with a worse outcome of PJI treatment include: infections caused by *Staphylococcus* spp.[36], and more specifically by *Staphylococcus aureus*[173,174,214,217], polymicrobial PJI[42], intra-articular purulence[36], retention of exchangeable components[42], and longer time between initial arthroplasty and PJI diagnosis[42,200,217,232]. Most PJI are caused by coagulase-negative *Staphylococcus* (30–41%) and *S. aureus* (12–47%). *Streptococcus* spp. And *Enterococcus* spp. are less common causes, both at around 10% of the total, as are gram-negative bacteria such as *Escherichia coli* (< 5%)[144,173,233]. A prevalence of 5–39% has been described for polymicrobial infections[36,42,174,203,233].

A regimen of debridement, antibiotics, irrigation and implant retention (DAIR) is generally accepted for acute infections without complicating factors such as significant comorbidity or loosening of the prosthesis. DAIR has shown varying success rates: as low as 14%[15] and as high as 100%[194]. Success can be achieved in over 70% of the cases when patients with favorable factors are selected, such as those with short duration of symptoms (less than 3–4 weeks), a stable implant, and healthy soft tissues surrounding the prosthesis[8,173,195,214,234]. In the case of chronic infections, implant retention is rarely successful. Implant removal leaves the patient disabled for weeks or even months[8].

Local antibiotic treatment, with aminoglycosides in beads or sponges, could theoretically reach high local concentrations without exposing the patient to toxic serum levels. Beads have a prolonged release compared to sponges but do not reach such high concentrations[130]. These can also act as foreign bodies, to which bacteria might adhere[43].

We evaluated the outcome of DAIR for total hip and knee PJI in three Dutch hospitals, to study factors associated with successful outcome and to study the outcomes of the use of local antibiotic carriers.

Methods

Study design

This was a retrospective cohort study, with a follow-up of at least 2 years or until the patient died. PJI was defined according to Crockarell *et al*.[15], and required one or more of the following criteria:

- (I) growth of the same microorganism in at least 2 culture specimens (preoperative joint aspiration and/or intraoperative, intracapsular specimen);
- (II) 1 positive culture, and intracapsular purulence during debridement procedure, acute inflammation on histopathological examination of intraoperative specimen, and/or an actively draining sinus tract;
- (III) culture-negative infection: negative culture results and at least 2 of intracapsular purulence during debridement procedure, acute inflammation on histopathological examination of intraoperative specimen, and an actively draining sinus tract.

The study population consisted of 91 patients who were treated with DAIR for PJI of total hip arthroplasty (THA) or total knee arthroplasty (TKA) at three Dutch hospitals between January 2004 and December 2009. 34 Of the patients with PJI of the hip have already been described and were also included[115].

Treatment

The decision for or against DAIR treatment was made by the treating surgeon, in consultation with the orthopedic team. It was based on clinical signs and symptoms, type of infection, and absence of radiographic loosening. DAIR was repeated after 2 weeks if clinical symptoms and laboratory signs did not improve. The decision to remove the implant was made individually by the surgeon in consultation with the patient.
The decision to use local antibiotic carriers was made by the treating surgeon. Carriers were either gentamicin beads (Septopal; gentamicin sulfate in polymethylmethacrylate, 225 mg per chain; Biomet, Germany) or gentamicin sponges (Garacol; gentamicin sulfate in equine collagen, 130 mg per sponge; EusaPharma, UK). Antibiotic therapy, based on bacterial susceptibility and in consultation with either an infectious diseases specialist or a medical microbiologist, was administered for at least 6 weeks.
The joint was opened through the old scar or wound, and after tissue collection for multiple cultures (at least 3) from synovium, capsule, and interfaces, was thoroughly debrided, including synovial resection. Exchangeable components were replaced in most cases, but this was not standard procedure. After debridement, the joint and wound were meticulously irrigated with saline using pulsed lavage, and primarily closed. No drains or vacuum systems were used. Removal of gentamicin beads was always combined with debridement, and was therefore counted as a procedure. Postoperatively, antibiotic treatment was started, either with a broad range agent such as vancomycin (Vancomycin; Xellia Pharmaceuticals ApS, Denmark), or—when the causative species was known—an agent based on susceptibility. A thromboprophylactic agent (Nadroparin) was administered during the hospital stay.

Outcome

A successful treatment outcome was defined as the absence of clinical and laboratory signs of inflammation (C-reactive protein blood serum levels of < 10 mg/L) at a follow-up of 2 years. Patients who required chronic, suppressive antibiotic treatment, who underwent prosthesis removal, or who died within this 2-year period were considered to be cases of treatment failure.

Statistics

The assumption of normality was checked by visual inspection of the histograms, q-q plots, and box plots of the data. A Kolmogorov-Smirnov test was also performed on the data. For continuous variables with a normal distribution, mean and standard deviation (SD) are given, whereas variables that were not normally distributed are given as median and interquartile range (IQR). To determine whether patients with successful treatment differed significantly from patients with unsuccessful treatment, independent t-tests

were performed for continuous variables with normal distribution and the non-parametric Mann-Whitney U-test was used for continuous variables without normal distribution. For categorical variables, chi-square tests were performed for large groups and Fisher's exact test was used for small groups. Variables that were statistically significantly different between success and failure groups were subsequently analyzed with logistic regression to correct for confounding. Kaplan-Meier analysis was used to describe the infection-free survival (with treatment failure as endpoint).
All statistical analyses were performed with IBM SPSS Statistics 20.0 and p-values < 0.05 were considered statistically significant.

Results

Population and patient characteristics

91 patients with PJI (62 hips, 29 knees) were treated with DAIR, 60 of whom were free of infection without resection arthroplasty or use of suppressive antibiotics at follow-up: a 66% success rate. Factors analyzed for the success and failure groups are summarized in Table 1.
16 patients died during follow-up. Nine had a follow-up of at least 2 years, eight of whom were treated successfully and one of whom died 32 months after revision surgery. Seven patients died within 2 years of follow-up and they were considered treatment failures. Two of these patients were free of symptoms when they died. Two deaths were infection-related: one patient died of sepsis and one patient refused further treatment, both within 3 months of the start of symptoms (Figure 1). No other permanent complications were seen. Seven patients developed high creatinine levels during treatment, but renal function normalized in all seven in the months that followed.
Mean duration of follow-up was 35 (0–79) months. See Figure 1 for a flow chart of surgical treatment in this study, and Figure 2 for infection-free survival.

Factors associated with outcome

In univariate analysis, eight factors were statistically significantly associated with treatment failure (Table 1). After logistic regression analysis, five factors were associated with failure: rheumatoid arthritis, late infection, ESR at presentation above 60 mm/h, symptom duration of more than 7 days before the start of treatment, and PJI caused by coagulase-negative Staphylococcus (Table 1). Revision arthroplasty was not associated with either treatment failure or success.

Surgical treatment

The mean number of procedures was similar in successfully and unsuccessfully treated patients (Table 1). No difference in success rate was seen between patients who underwent one DAIR procedure and patients who underwent multiple procedures.
The use of gentamicin sponges was statistically significantly higher in the success group, and the use of beads was significantly higher in the failure group. These dif-

Variable	Success, n=60	Failure, n=31	p (univariate)	p (adjusted)	OR
Demographics					
Age in years: mean (SD)	70 (11)	b	0.7		
Female sex	37	17	0.5		
Hip joint	38	24	0.2		
Knee joint	22	7	0.2		
Infection after revision surgery	12	8	0.5		
Cemented arthroplasty	22	20	0.01*	0.7	0.3-7.3
Comorbidities					
Cardiac	31	16	1.0		
Pulmonary	5	6	0.2		
Renal insufficiency	6	0	0.09		
Diabetes	7	6	0.4		
Rheumatoid arthritis	3	7	0.03*	0.03*	1.2-84*
Malignancy	4	3	0.7		
Clinical presentation					
Duration of symptoms in days: median (IQR)	3 (5)	6 (7)	0.02*		
Symptoms <1 week	44	16	0.02*	0.05*	1.0-18*
Symptoms <3 weeks	54	25	0.1		
Time from arthroplasty to presentation in days: Median (IQR)	21 (51)	42,5 (266)	0.05*		
Early infection (<3 months)	48	19	0.06		
Delayed infection (3-24 months)	10	7	0.5		
Late infection (>2 years)	2	5	0.04*	0.04*	1.1-366*
Type 1 (early postoperative)	38	14	0.2		
Type 2 (chronic)	3	4	0.2		
Type 3 (acute hematogenous)	19	13	0.3		
CRP at presentation (mg/L): mean (SD)	164 (119)	155 (118)	0.7		
ESR at presentation (mm/hour): mean (SD)	54 (26)	76 (27)	0.002*		
ESR >60 mm/hour	19/47	20/24	0.001*	0.005*‡	2.2-98*
Surgical treatment					
Number of procedures: mean (SD)	2.0 (0.8)	2.4 (1.5)	0.1		
Single DAIR procedure	21	11	1.0		
Multiple DAIR procedures	39	20	1.0		
Gentamicin sponges used	48	16	0.005*	0.4	0.05-2.9
Gentamicin beads used	4	8	0.02*	1.0	0.06-18
Sponges and beads used	2	4	0.2		
No local antibiotic use	6	3	1.0		
Microbiology (including polymicrobial infections)					
CNS	4	9	0.009*	0.02*	1.8-309*
Staphylococcus aureus	34	16	0.6		
Streptococcus spp.	10	1	0.09		
Escherichia coli	3	1	1.0		
Enterobacter cloacae	2	2	0.6		
Enterococcus faecalis	5	0	0.2		
Other	7	2	0.7		

Table 1: Patient characteristics and variables of a cohort treated with debridement, antibiotics, irrigation and implant retention (DAIR), divided by success or failure of treatment; OR: odds ratio; SD: standard deviation; IQR: interquartile range; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; CNS: coagulase-negative Staphylococcus; *p-value <0.05; ‡ESR as continuous and ESR as dichotomous value are the same variable: only the clinically more useful dichotomous ESR with a cutoff of 60 mm/hour was analyzed by logistic regression.

ferences were not significant in the logistic regression analysis. The mean number of procedures was lower when sponges were used (2.0, SD 0.8) than when beads were used (2.8, SD 1.4) (p = 0.006).

Microbiology

Preoperative aspiration was performed in 65 patients, and a causative microorganism

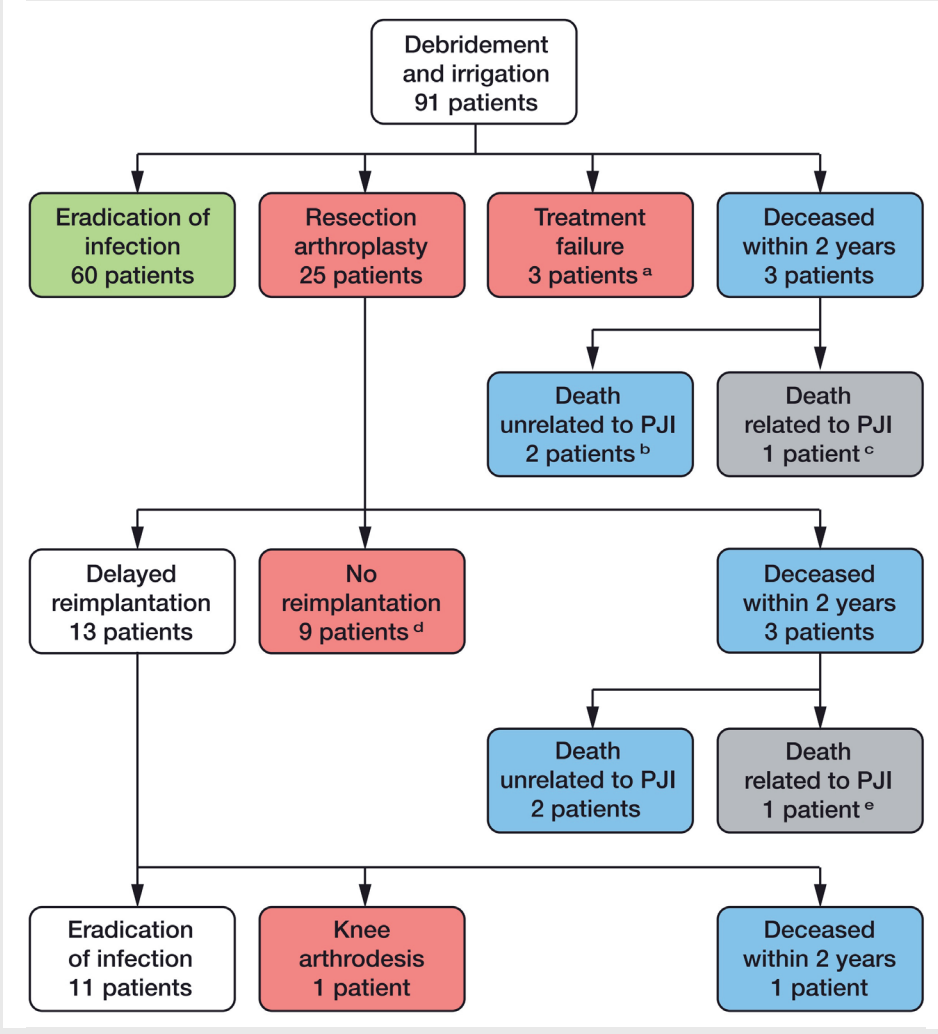


Figure 1: Flow chart of surgical treatment of patients included in the study; PJI: periprosthetic joint infection.
[a] 3 patients had a chronic low-grade infection, of which 1 used antibiotic agents chronically.
[b] 2 patients had no infectious symptoms (but were assigned to 'failure' as adequate follow-up was not possible).
[c] 1 patient refused further surgical and antibiotic treatment and died 19 days after debridement and irrigation procedure.
[d] 2 knee arthrodeses; 1 above knee amputation after failed arthrodesis; in 6 patients the resection situation was accepted.
[e] 1 patient died 14 days after prosthesis removal due to sepsis.

was found in 60 of them. Intraoperative samples were collected from all 91 cases, which yielded at least one positive result in 87 patients. For the other four patients, aspiration fluid yielded positive cultures. No culture-negative infections were seen.
Most infections were caused by S. aureus (Table 1). MRSA was responsible for only two cases of PJI, both of which were treated successfully. PJI caused by coagulase-negative Staphylococcus was associated with a low success rate and streptococcal infec-

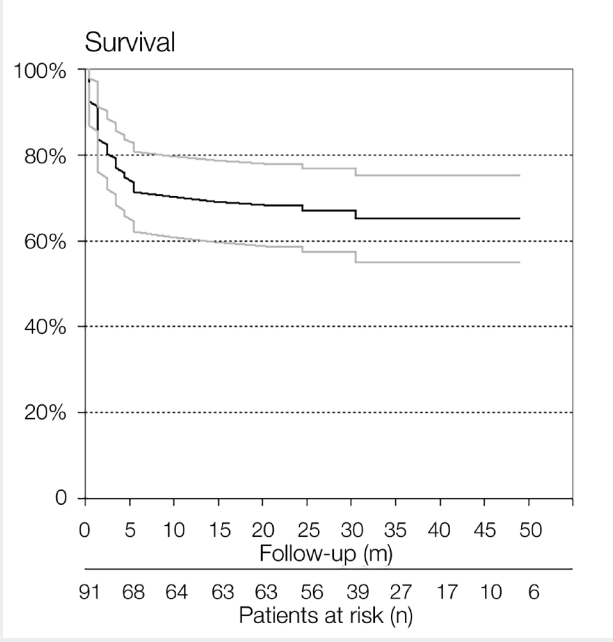


Figure 2: Kaplan-Meier survival analysis (percentage of patients free of infection) of 91 patients treated with debridement, antibiotics, irrigation and implant retention (DAIR). Red lines show 95% confidence intervals.

tions were associated with a high success rate. All streptococcal infections were treated within 1 week of onset of symptoms. Five patients had a polymicrobial periprosthetic joint infection; all were treated successfully.

Discussion

Demographics and comorbidity

Of the 91 patients included in this study, 60 were treated successfully with DAIR. Revision arthroplasty has been described by others as a risk factor for PJI[173,230,231], but it was not associated with treatment failure in this cohort. Of all comorbidities described, only rheumatoid arthritis was found to be associated with PJI; this was also found in one other study[230]. Only two patients with rheumatoid arthritis were using immunosuppressive drugs (one in the success group and one in the failure group).

Clinical presentation

In most cases (60/91), treatment was started within 1 week of onset of infectious symptoms, which had a better outcome. The treatment success with early infections and infections of short duration of symptoms is commonly attributed to lack of biofilm formation[212], and it is strongly recommended that DAIR should only be used for patients

with a short duration of symptoms (less than 3 weeks) or time after initial arthroplasty of less than 30 days[8]. We found that having symptoms for less than 1 week was associated with treatment success.
Although usually discouraged, seven patients with a duration of symptoms of more than 4 weeks were treated with DAIR. In all cases, the decision to use DAIR was made by the treating surgeon because of early PJI occurring within 3 months after initial surgery[48]. We included these seven patients nonetheless, because this might further identify factors associated with outcome. Duration of symptoms of more than 4 weeks was not a factor associated with treatment outcome.
An ESR at presentation of more than 60 mm/h was associated with treatment failure. A low ESR at presentation could indicate a shorter duration of infection, and might therefore be predictive of a higher chance of success. Other studies have focused on the ability of these blood infection markers (CRP and ESR) to establish a diagnosis of PJI[235,236], and one study found that high CRP was predictive of failure[42], but to our knowledge ESR has never been described as a factor associated with treatment outcome.

Surgical treatment
In staged revision, gentamicin-loaded beads are often used to fill the dead space after arthroplasty removal, but evidence on their effectiveness is limited[43,130]. To our knowledge, their use in DAIR has never been studied. The use of gentamicin sponges in treatment of PJI has only been described in a few studies[115,130,185,237]. The report by Kuiper *et al.* includes 34 of the patients included in the present study[115].
A higher success rate for sponges and a lower success rate for beads was found in univariate analysis, but this was not confirmed in multivariate analysis. The use of gentamicin sponges was associated with fewer procedures.
The collagen-based gentamicin sponges used are biodegradable and do not need removal surgery, as opposed to beads. Furthermore, sponges reach higher local antibiotic concentrations than beads[130], and it has been suggested that beads are themselves foreign bodies and therefore maintain the infection[43]. Our cohort may have been too small to allow us to find statistically significant differences between the two antibiotic carriers, but selection bias must be considered as well: one might argue that beads were used in cases of severe infection, where additional debridement procedures were anticipated and needed.

Microbiology
We found that CNS infection was associated with treatment failure. Other authors have also described staphylococcal or, more specifically, *S. aureus* infection to have a higher risk of failure[36,173,214,217]. Possible explanations for this phenomenon are the ability of the species to form a biofilm, and the virulence of the causative microorganism: coagulase-negative *Staphylococcus* is known to be of low virulence, which may delay and impede the diagnosis.
Treatment of streptococcal infections had a high success rate, and they were all treated within 1 week after symptoms became apparent. That this was not a significant factor

may be explained by sample size, but the high success rate might also be explained by the short duration of symptoms. One study also found a correlation between streptococcal infections and good outcome[219].
Only five of 91 patients had an infection caused by multiple microorganisms, and all were free of infection at follow-up. Some authors have also found relatively few polymicrobial infections, between 5 and 10%[36,191], but others have described much higher rates of multi-organism PJI: between 19 and 39%[42,174,195,203,233]. All of these studies used culture to identify microorganisms, and no DNA techniques. Whether this difference is a matter of culture method or whether some other (regional) factor might be involved remains uncertain. Only one study found higher failure for polymicrobial infection, with a hazard ratio of 1.8[42].

Limitations

This was a retrospective study, with its inherent caveats for interpretation. The sample size may have been too small for identification of any weaker risk factors, and selection bias cannot be ruled out. Also, although comparable, the irrigation and debridement procedures and culture methods were not standardized in the different hospitals. The possible bias in the use of gentamicin beads and sponges has already been mentioned.

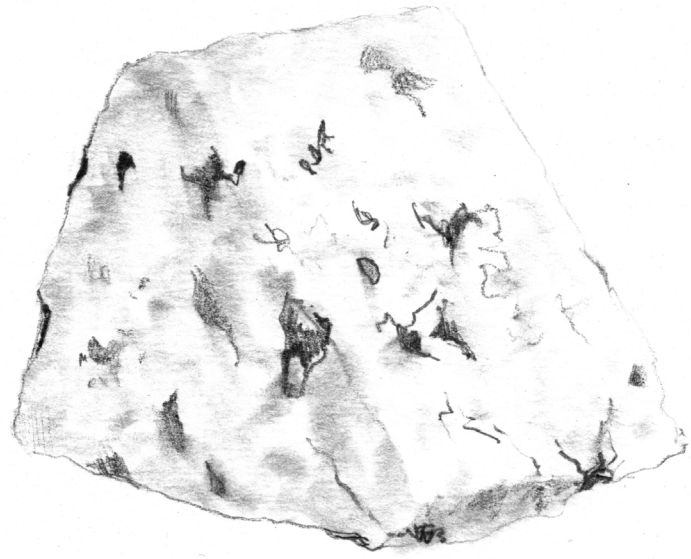
Conclusion

Several factors were associated with treatment failure: a history of rheumatoid arthritis, duration of symptoms of more than 1 week, late infection (more than 2 years after arthroplasty), ESR at presentation above 60 mm/h, and the presence of coagulase-negative *Staphylococcus.* When one or more of these factors is present in a patient, one should realize that the chances of successful DAIR treatment decrease. Furthermore, when local antibiotic carriers were used, gentamicin-loaded sponges—which do not require additional removal surgery— showed outcome results comparable to those with beads, but with fewer procedures. Prospective studies will be needed to evaluate their effect on PJI and biofilm formation.

TREATMENT
OF PERIPROSTHETIC JOINT INFECTIONS

CHAPTER **10**

Two-stage revision recommended for treatment of fungal hip and knee periprosthetic joint infections



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CHAPTER 10

Two-stage revision recommended for treatment of fungal hip and knee periprosthetic joint infections

Abstract

Fungal periprosthetic joint infections are rare and difficult to treat. This systematic review was conducted to describe outcome and give treatment recommendations.
After extensive literature research, and including 8 patients from our own institutions, 164 patients treated for fungal hip or knee periprosthetic joint infection (PJI) were included. Most patients presented with pain (78%) and swelling (65%). In 68% of the patients, one or more risk factors for fungal PJI were found. In 51% of the patients, radiographs showed signs of loosening of the arthroplasty. Candida species were cultured in most patients (88%). In 21% of all patients, fungal culture results were first considered contamination. Co-infection with bacteria was present in 33% of the patients. For outcome analysis, 119 patients had an adequate follow-up of at least 2 years. Staged revision was the most often performed treatment, with the highest success rate: 85%.
Fungal PJI resembles chronic bacterial PJI. For diagnosis, multiple samples and prolonged culturing are essential. Fungal species should be considered as a pathogen. Co-infection with bacteria should be treated with additional antibacterial agents.
No evidence was found that one-stage revision, debridement, antibiotics, irrigation and implant retention (DAIR) or antifungal therapy without surgical treatment adequately controls fungal PJI. Hence, two-stage revision should be the standard treatment for fungal PJI. After resection of the prosthesis, we recommend systemic antifungal treatment for at least 6 weeks and until there is absence of clinical signs of infection and blood infection markers have normalized. Thereafter, reimplantation can be performed.

Introduction

Periprosthetic joint infection (PJI) is the most debilitating and expensive complication following arthroplasty[104]. A nationwide study performed in the USA showed an infection burden of 1.23% for THA and 1.21% for TKA, a nearly twofold increase between 1990 and 2004[229].
Fungal PJI is uncommon, occurring in approximately 1% of all PJI[238,239]. Reports in literature are limited and most include only a small number of patients[238,240–242]. Most fungal PJI are caused by *Candida albicans* and *Candida parapsilosis*[238]. Extensive co-morbidity and decreased immunity are considered risk factors for fungal infections[238,239]. Surgical treatment options are similar to that of bacterial PJI[238]. The Infectious Diseases Society of America recommends removal of the arthroplasty in most patients, with therapy for at least 6 weeks with fluconazole or amphotericin B[8]. If removal of the arthroplasty is not an option, for instance due to the poor health of the patient, chronic suppression with fluconazole is recommended[243].

This review includes 158 previously reported cases of fungal hip and knee PJI and 8 patients from our own institutions. Treatment options and outcome are analyzed.

Methods

The following online databases were searched: Medline (period 1966 to July 2012), Cochrane Clinical Trial Register (1988 to July 2012) and Embase (January 1988 to July 2012). The search was independently performed by 2 reviewers (JK and SC). Disagreement was resolved by consensus and third-party adjudication.
Using the search terms "prosthesis implantation[Mesh]" AND "candida[Mesh]", "(candida OR fungal) AND (((hip OR knee OR shoulder) AND prosthesis) OR arthroplasty)", "(candida OR fungal) AND (prosthesis OR arthroplasty) NOT Medline[sb]", we initially found 1411 articles. The titles, abstracts and keywords of these papers were reviewed and the full publications were retrieved if there was insufficient information to determine appropriateness for inclusion. All publications considered relevant were read completely. Additionally, references of included publications were checked for articles that were initially missed. Articles that were not written in English were included if translation was possible.
Additionally, we retrospectively studied patient files from all patients who were treated for fungal periprosthetic joint infection in our institutions between 2003 and 2011.
Collected data from all included articles and patients from our own institutions included: age, sex, affected joint, primary or revision surgery, co-morbidity, preoperative diagnosis, symptoms, duration of symptoms, interval between primary surgery and onset of symptoms of infection, species isolated, origin of culture samples (i.e. aspiration, intraoperative, other), other cultured microorganisms, fungal cultured considered irrelevant (yes or no), C-reactive protein (CRP, mg/L) and erythrocyte sedimentation rate (ESR, mm/hour) at presentation, radiographic findings, local and systemic antimicrobial therapy, duration of antimicrobial therapy, type of surgical treatment, time from resection to reimplantation, outcome, and duration of follow-up.

Definitions

Risk factor status was based on risk factors previously mentioned by others: an immunosuppressive or immunodeficient status, diabetes mellitus, rheumatoid arthritis, tuberculosis, a history of renal transplantation, drug abuse, prolonged antibiotic use, indwelling catheters, malnutrition, severe burns, multiple abdominal surgeries, prior PJI, revision surgery, and cutaneous candidiasis[238,240,241,244–247].
Since criteria used to define infection were not always clearly noted by other authors, we decided to consider all fungal infections described in the individual studies as definite fungal infections.
Cure of fungal PJI is defined as good clinical function and absence of infectious signs and symptoms, with the arthroplasty present (either after staged revision or after debridement), without the use of chronic antifungal or antibacterial therapy and with a follow-up of at least 2 years.

	Study	Language	N	Joint	Type
1	Acikgoz 2002[249]	English	1	Knee	Case report
2	Anagnostakos 2012[241]	English	7	Hip & knee	Case series
3	Antony 2008[250]	English	1 of 2	Hip	Case series
4	Austen 2013[251]	English	1	Knee	Case report
5	Austin 1992[252]	English	1	Knee	Case report
6	Azzam 2009[238]	English	31	Hip & knee	Retrospective cohort study
7	Badrul 2000[253]	English	1	Knee	Case report
8	Baumann 2001[254]	English	1	Knee	Case report
9	Bland 2009[255]	English	1	Knee	Case report
10	Brooks 1998[256]	English	1	Knee	Case report
11	Bruce 2001[257]	English	2	Hip	Case series
12	Cardinal 1996[258]	English	3	Hip	Case series
13	Chiu 2013[247]	English	1	Hip	Case report
14	Cushing 1997[259]	English	1	Knee	Case report
15	Cutrona 2002[260]	English	1	Hip	Case report
16	Darouiche 1989[261]	English	4	Hip & knee	Case series
17	Deelstra 2012[262]	English	1	Hip	Case report
18	DeHart 1995[263]	English	1	Knee	Case report
19	Dumaine 2008[264]	English	1	Knee	Case report
20	Dutronc 2010[240]	English	7	Hip & knee	Case series
21	Evans 1990[265]	English	2	Hip	Case series
22	Fabry 2005[266]	English	1	Knee	Case report
23	Fowler Jr. 1998[267]	English	1	Hip	Case report
24	Fukasawa 1997[268]	English	1	Knee	Case report
25	Garcia-Oltra 2011[245]	Spanish	8 of 10	Hip & knee	Case series
26	Gaston 2004[269]	English	1	Knee	Case report
27	Goodman 1983[270]	English	2	Hip & knee	Case series
28	Gottesman-Yekutieli 2011[271]	English	1	Hip	Case report
29	Graw 2010[272]	English	2	Knee	Case series
30	Guyard 2006[273]	French	1	Hip	Case report
31	Hennessy 1996[274]	English	1	Knee	Case report
32	Hwang 2012[242]	English	30	Knee	Retrospective cohort study
33	Iskander 1988[275]	English	1	Knee	Case report
34	Johannsson 2009[276]	English	1	Hip	Case report
35	Kelesidis 2010[244]	English	1	Hip	Case report
36	Koch 1988[277]	English	1	Knee	Case report
37	Kuberski 2011[248]	English	2 of 6	Hip & knee	Case series
38	Lackner 2011[278]	English	1	Knee	Case report
39	Lambertus 1988[279]	English	2	Hip & knee	Case series
40	Langer 2003[280]	English	1	Knee	Case report
41	Lazzarini 2004[281]	English	1	Hip	Case report
42	Lejko-Zupanc 2005[282]	English	1	Hip	Case report
43	Lerch 2003[283]	English	1	Knee	Case report
44	Levine 1988[284]	English	1	Knee	Case report
45	MacGregor 1979[285]	English	1	Knee	Case report
46	Marra 2001[286]	English	1	Hip	Case report
47	Merrer 2001[287]	English	1	Hip	Case report
48	Moisés 1998[288]	Spanish	1	Hip	Case report
49	Nayeri 1997[289]	English	1	Hip	Case report
50	Paul 1992[290]	English	1	Knee	Case report
51	Phelan 2002[239]	English	4 of 10	Hip & knee	Case series
52	Prenzel 2003[291]	German	1	Hip	Case report
53	Ramamohan 2001[292]	English	1	Hip	Case report
54	Selmon 1998[293]	English	1	Knee	Case report
55	Simonian 1997[294]	English	1	Knee	Case report
56	Tunkel 1993[295]	English	1	Knee	Case report
57	Villamil-Cajoto 2012[296]	English	1	Knee	Case report
58	Wada 1998[297]	English	1	Knee	Case report
59	White 1995[298]	English	1	Knee	Case report
60	Wu 2011[246]	English	1	Knee	Case report
61	Wyman 2002[299]	English	1	Knee	Case report
62	Yang 2001[300]	English	1	Knee	Case report
63	Yilmaz 2011[301]	English	1	Knee	Case report
64	Younkin 1984[302]	English	1	Hip	Case report

Table 1: Studies included in this review, describing hip and knee fungal periprosthetic joint infection.

Baseline data, such as patient characteristics and culture results, are not only described for patients with a follow-up of at least 2 years, but for all included patients.

Included studies

68 studies describing fungal hip and knee PJI were found. Two out of 10 patients were excluded in a group of fungal PJI patients described, because the infected joint was unclear[245]. From one study, four of six patients were excluded, as fungal infection of the native joint was proven or strongly suspected before arthroplasty[248]. One article described 10 patients, of which six patients had already been reported[239]. In total, 64 studies were included, describing 156 patients (Table 1). We included eight more patients from our own institutions (Table 2), amounting to a total of 164 patients.

Results

Patient characteristics

164 patients were included (63% female). 94 patients had a fungal infection of a knee arthroplasty and 70 of a hip arthroplasty. Infection occurred after primary arthroplasty in 68 patients, after revision arthroplasty in 53 patients, and in 43 patients primary or revision arthroplasty was not specified. In 17 patients, the duration of follow-up was not reported, and in 32 patients follow-up was less than 2 years, leaving 119 patients with a follow-up of at least 2 years (Figure 1).

Possible risk factors predisposing PJI were accurately described in 148 patients: 101 patients had one or more risk factors for PJI (68%) (Table 3).

Clinical features and diagnosis

Clinical symptoms were described for 147 patients. Most patients presented with symptoms of chronic infection like pain (78%) and swelling (65%). Other symptoms included warmth (18%), limited range of motion (10%), redness (8%) and fever (7%). Wound drainage and sinus tract were described in 4% and 9% of patients, respectively.

The mean duration from last performed arthroplasty (primary or revision) to diagnosis of fungal PJI was 27 months (2 weeks - 22 years). 29% of the patients had an infection free period of at least 2 years after index surgery.

Plain radiography results were described in 118 patients. In 60 patients, signs of loosening of the prosthesis were seen (“loosening”, “lucency”, and “osteolysis”).

C-reactive protein blood levels (CRP, mg/L) and erythrocyte sedimentation rate (ESR, mm/hour) were available in 91 and 101 patients, respectively. In 4 reports, the unit of CRP blood levels was not mentioned, and these were left out (some authors reported in mg/L, others in mg/dL). Mean CRP levels at presentation were 44 (0.9-280) mg/L, mean ESR was 53 (7-141) mm/hour.

The final diagnosis was always based on culture results, from aspiration fluid alone (n=32), intraoperative specimens alone (n=45), or aspiration and intraoperative specimens combined (n=32). In three patients, the fungus was detected intraoperatively and

	Age	Sex	Co-morbidity	Joint	Primary/revision	Diagnosis	Symptoms	Time surgery to PJI diagnosis (m)
1	62	M	DM, gout, obesity, cutaneous candida	Hip	Revision	Recurrent dislocations	Pain, swelling, redness, shivering	27
2	81	F	Obesity, tuberculosis in past	Hip	Revision	Fracture	Pain, swelling	24
3	73	F	DM, obesity, cutaneous candida	Hip	Primary	Avascular necrosis	Pain, swelling, skin necrosis	1.5
4	78	F	DM	Hip	Primary	Fracture	Pain, redness, fistula	10
5	70	F	-	Hip	Revision	Osteoarthritis	Pain, subluxations	14
6	80	F	Renal disease, chronic wound infection with fistula, candida infection of catheter, obesity	Hip	Revision	Osteoarthritis	Pain	13
7	80	F	Cardiac disease, obesity	Hip	Primary	Fracture	Pain, redness, swelling, shivering	1.5
8	58	M	Multiple sclerosis, metastatic malignancy with pelvic radiotherapy and chemotherapy	Hip	Revision	Fracture	Pain, shivering, vomiting, diarrhea	14

	Species	Culture origin	Considered contamination	Other cultures	CRP (mg/L)	ESR (mm/hour)	Radiographic findings
1	*Candida albicans*	Intraoperative	Yes	MSSA, *Staphylococcus capitis*	77	53	No loosening
2	*Candida albicans*	Intraoperative	No	CNS	21	-	No loosening
3	*Candida albicans*	Intraoperative	Yes	CNS, *Enterococcus faecalis*	116	83	No loosening
4	*Candida albicans*	Sinus tract + intraoperative	No	MSSA	15	22	No loosening
5	*Candida albicans*	Aspiration	No	CNS, *Corynebacterium* species, *Streptococcus viridans*	25	110	Osteolysis
6	*Candida glabrata, Candida albicans*	Intraoperative	No	MSSA	42	140	Loosening
7	*Candida albicans*	Intraoperative	Yes	MSSA, CNS	67	-	No loosening
8	*Candida parapsilosis*	Aspiration	No	*Streptococcus mitis*, CNS	13	25	No loosening

	Spacer	Antifungal therapy	Duration	Initial treatment	Second treatment	Time to reimplantation	Outcome	Follow-up (m)
1	No	Fluconazole	6 months	DAIR	Resection arthroplasty	-	Resection arthroplasty	12
2	Yes	Fluconazole	2 months	Resection arthroplasty	Reimplantation	4	Cured	32
3	Yes (GM, VM)	None	-	DAIR	Resection arthroplasty	-	Resection arthroplasty	95
4	Yes (GM)	Fluconazole	6 days	DAIR	-	-	Deceased	1
5	No	Fluconazole	5 months	Resection arthroplasty	Reimplantation	4	Resection arthroplasty	43
6	No	Caspofungin	6 weeks	Resection arthroplasty	Reimplantation	14	Deceased	7
7	Yes (GM)	Fluconazole	7 days	Resection arthroplasty	Reimplantation	4	Cured	45
8	Yes (GM, VM)	None	-	Resection arthroplasty	-	Not performed	Refused further treatment	8

Table 2: Characteristics of eight additional patients from our own institutions with fungal periprosthetic joint infection; DM: diabetes mellitus; PJI: periprosthetic joint infection; MSSA: methicillin sensitive Staphylococcus aureus; CNS: Coagulase-negative Staphylococcus; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; GM: gentamicin; VM: vancomycin; DAIR: debridement, antibiotics, irrigation and implant retention.

Risk factor	Number of patients (of 148 total patients)
None	47
Diabetes mellitus	38
Malignancy	10
Renal disease	8
Rheumatoid arthritis	20
Immunosuppression	23
Prior PJI	20

Table 3: Numbers of patients with risk factors for fungal periprosthetic joint infection (PJI), out of a total cohort of 148 patients.

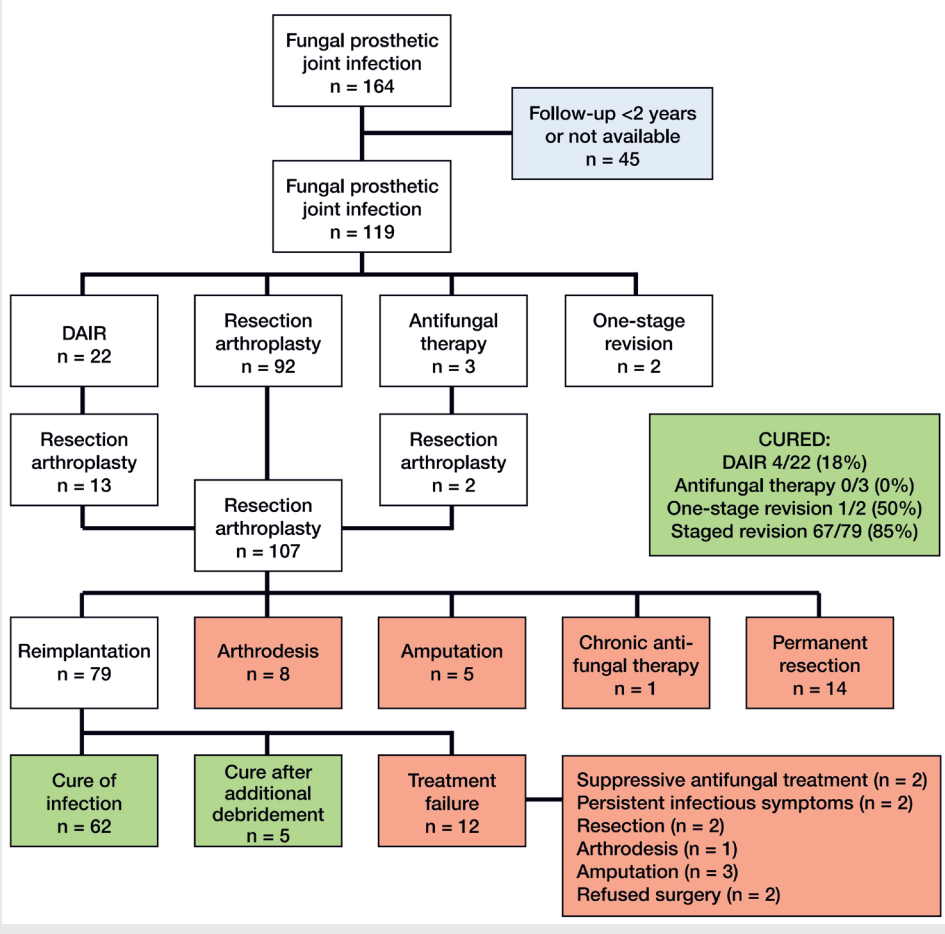

Figure 1: Flowchart describing the outcome of surgical treatment in 119 patients of fungal hip and knee periprosthetic joint infection with an adequate follow-up; DAIR: debridement, antibiotics, irrigation and implant retention.

with another method (one blood culture, one wound drainage, one sinus tract).
In 51% of the patients (n=84) it was reported whether the initial fungal cultures were considered as contaminants or not. In 18 patients (21%) the fungal cultures were initially considered as contamination.

Microbiology

Most fungal PJI were caused by *Candida* species (n=145; 88%), the commonest being *Candida albicans* (n=78; 48%). Other *Candida* species were *C. parapsilosis* (n=40), *C. glabrata* (n=14), *C. tropicalis* (n=6), *C. pelliculosa* (n=3), *C. lipolytica*, *C. guillermondii*, *C. famata*, and *C. lusitaniae* (all n=1). Five patients had polyfungal infections, all caused by *Candida*. Other fungal species were found in 24 patients and included species such as *Aspergillus fumigatus*, *Pichia anomala* and *Rhodotorula minuta*.
In 54 patients, bacteria were also cultured (33%). Coagulase negative *Staphylococcus* was cultured in 26 patients, methicillin sensitive *Staphylococcus aureus* (MSSA) in 13 patients, and methicillin resistant *Staphylococcus aureus* (MRSA) in 7 patients.

Surgical treatment

The number of patients in the different treatment groups are shown in Figure 1. Staged revision was successful in most patients (85%). Debridement, antibiotics (antifungals), irrigation and implant retention (DAIR) was successful in four of 22, one-stage revision in one of two patients and antifungal treatment without surgery in none (of three) patients. The mean interval between resection and reimplantation was 4.8 months, ranging from 1 week to 1.5 years. In 55 patients with staged revision, interval duration and treatment outcome were both described, of which only three patients in whom treatment failed (mean interval for success 4.2 months versus 2.8 months for failure). Interval duration of 6 weeks or less was described for five patients (all healed), 2 months or less for 19 patients (all healed), and 3 months or less for 34 patients (32 healed).
The use of a spacer was described in 86 patients. 68 spacers were loaded with antibiotic agents, five with antifungal agents, and seven with both. The exact doses of antifungal agents were mentioned by seven authors. Antifungal drugs used were amphotericin B in nine patients (between 187,5 mg and 1200 mg per batch of bone cement (40 grams)), amphotericin B and voriconazole in one patient (250 mg and 1000 mg per batch, respectively), fluconazole in one patient (200 mg in a spacer) and itraconazole in one patient (250 mg in a spacer). In two patients, fluconazole loaded bone cement beads were implanted (2000 mg per batch of bone cement).

Antifungal therapy

160 of 164 patients were treated with systemic antifungal agents, mostly with amphotericin B (71 patients) or fluconazole (80 patients). A combination of both was used in four patients. All fluconazole use was described in studies after 1996 (70/80 patients between 2002 and 2012). Amphotericin B was more frequently used in earlier studies (44/71 patients between 2002 and 2012). The use of echinocandins, a new group of antifungal agents, was described in six patients (2005-2012): caspofungin in three, micafungin in two, and anidafungin in one patient.

In 143 patients, the total duration of antifungal treatment was mentioned (intravenous and oral combined), with a mean of 3.8 (0-36) months. Seven other patients received chronic antifungal therapy at follow-up.
54 patients who underwent a staged revision had a follow-up of more than 2 years, and adequate description of antifungal treatment duration, of which 48 were treated successfully. Failures (n=6) had antifungal therapy for a mean of 5.7 (2.5-12) months. Successfully treated patients were administered antifungal agents for a shorter period (mean 2.9 months).
Antifungal agent administration of 0-6 weeks was described in 13 patients (n=13), with success in all. 0-2 months was reported in 28 patients, who all healed. 0-3 months was described 40 patients (38 healed), and 0-6 months in 48 patients (44 healed).

Discussion

Risk factors

Risk factors usually associated with fungal infections, more specifically with candidiasis, are mostly factors related to co-morbidity with an impaired immune response: an immunosuppressive or immunodeficient status, diabetes mellitus, rheumatoid arthritis, tuberculosis and/or a history of renal transplantation[238,241,244]. Other, external factors include drug abuse, prolonged antibiotic use, indwelling catheters, malnutrition, severe burns and multiple abdominal surgeries[238,241,244]. These factors are assumed to play a role in fungal periprosthetic joint infection also, as well as prior PJI, revision surgery, and cutaneous candidiasis[36,240,241,244–247]. Azzam *et al*. showed that around 50% of patients with fungal PJI had one or more risk factors, including cardiac disease[238]. However, we found that 101 of 148 patients had one or more risk factors for fungal PJI (68% of the patients), not including cardiac disease as a risk factor. Including cardiac disease, 82% of the patients were at risk (122/148).

Clinical features and diagnosis

The route of infection for fungal PJI remains controversial. The mechanism and clinical features often mimic that of chronic bacterial infection, with an indolent onset, and most often patients present with swelling and pain without other infectious symptoms[238,240,247,261,283]. Prosthetic loosening is seen in many patients, as the infection may have been lingering for years[256,279]. We found that half of the patients had radiographic signs of loosening. This is comparable to patients with bacterial PJI[303]. As fungal PJI develops slowly, diagnosis is difficult, and the diagnosis ‘aseptic loosening’ is easily made, especially without bacterial co-infection[283].
Most authors agree that serum values, such as CRP and ESR, and joint fluid cell counts have limited value. The discrimination between fungal and bacterial PJI is impossible based on laboratory values. The value of additional tests, such as bone scintigraphy and serum titers, remains unclear[241,244,290].
The diagnosis should be based on cultures from aspiration fluid or operatively obtained

tissue or swabs. However, a substantial delay in diagnosis may occur because culture results are sometimes seen as contaminants, and most authors suggest obtaining multiple samples, prolonged culturing and special staining[238,240,247,292,300]. Furthermore, if *Candida* species are cultured, these should always be treated as a pathogen, according to Dutronc *et al.*[240]. We found that in 21% of the patients the fungal culture result was - incorrectly - considered contamination. We recommend always considering a cultured fungal species as a pathogen.
Because diagnosis with the above-mentioned microbiological methods may be difficult, other methods, such as polymerase chain reaction (PCR) may be useful. However, none of the articles concerning fungal PJI mentions PCR.

Treatment
Primary antifungal drug treatment, without surgical treatment, was described in only 3 patients with adequate follow-up, of which none healed. DAIR was successful in four of 22 patients. For bacterial PJI, the consensus is that chronic infections should never be treated with DAIR[8,15]. We suggest the same for fungal PJI.
One-stage revision, performed in two patients, was successful in one, and unsuccessful in another patient[293,294]. These numbers are too small to draw any conclusions on one-stage revision as an alternative to two-stage revision for fungal PJI.
Many authors treat fungal PJI as a chronic bacterial infection, and staged revision is generally recommended[238,240,247,261,283]. In our series, this treatment was the most common, with a success rate of 85% (67/79 patients). The success rate of two-stage revisions for bacterial PJI is approximately 87-91%[304–306].
The ideal interval between implant removal and reimplantation is unknown. We found a mean of 4.8 months, with a range from 1 week to 1.5 years. Some authors suggest a 3-month period[265,300], others advise reimplantation only when repeated (aspiration) cultures are negative[239,247]. In only three patients with failure of staged revision the time between resection and reimplantation arthroplasty was mentioned (mean 2.8 months, versus 4.2 months in the successfully treated patients). The group of patients in which the interval was adequately mentioned may not be representative for the whole group of fungal PJI patients. Apart from a minimum of 6 weeks, we do not dare to make recommendations on the duration of the resection reimplantation interval. We therefore recommend reimplantation to be performed only in absence of clinical signs of infectious symptoms, and CRP and ESR serum levels within the normal range (CRP <5.0 mg/L and ESR <10 mm/hr) or showing continuously lowering values.
The use of local antifungal treatment was described in 14 patients (2 beads, 12 spacers)[239,246,257,262,269,271,286,293]. Two authors report high local levels of antifungal agent with this method[257,286], but others claim local antifungal therapy has no effect, based on laboratory studies[238,299]. An antibiotic loaded spacer to treat bacterial co-infection or prevent bacterial super-infection, was used in 75 patients[238,241,262]. No specific recommendations about the use of antifungal treatment in cement can be made because of the low number of patients. However, adding antibiotics to the cement is advised because of the high number (33%) of patients with a combined fungal and bacterial PJI.

Antifungal therapy

Most authors suggest a minimum treatment duration of 6 weeks[239,241,292], but others advise a minimum of 12 months[238,251]. Amphotericin B or fluconazole are considered the drugs of choice for administration in fungal infections[250,251,269]. All fluconazole treatments were described in studies reported after 1996, when the use of amphotericin B diminished. This can be explained by the time of development of the products, and the publication of studies that indicate that fluconazole is as effective for hematogenous candidiasis, yet better tolerated than amphotericin B[307]. Amphotericin B is one of the most toxic antimicrobial drugs, with a high incidence of adverse effects[287]. On the other hand, primary resistance against fluconazole is common in some non-albicans *Candida* species, particularly *Candida krusei* and *Candida glabrata*[293,308].

The use of echocandins was only described in a few reports[255,264,272,282], but may be a good alternative, due to its low toxicity and broad spectrum, especially treating fluconazole resistant fungal species, or if amphotericin B is not tolerated by the patient. However, long term side effects are unclear[244].

The period of antifungal treatment was shorter in successfully treated patients, compared to patients with treatment failure. This might be due to several factors, including selection bias (e.g., patients in a worse condition may be treated longer) and publication bias (e.g., patients cured with a short antifungal period may be more interesting to publish). The possibility that longer treatment actually does worse on treatment outcome seems illogical. However, longer treatment may be bothersome for some patients. We concur with other authors, and because duration (comparing 6 weeks and 3 months of antifungal treatment) does not seem to influence outcome after reimplantation, we recommend antifungal treatment for at least 6 weeks, which may be extended until serum CRP and ESR levels have normalized or show continuously lowering values, and clinical signs of infection remain absent. There is no evidence that a shorter period of antifungal treatment has the same results.

Conclusion

68% percent of the patients with fungal PJI had one or more risk factors predisposing for fungal PJI. The majority of these patients presented with signs and symptoms similar to chronic bacterial PJI, such as pain, swelling and prosthetic loosening. The diagnostic tools are the same for both kinds of infection, recommended by the Workgroup of the Musculoskeletal Infection Society[17]. Fungal culture results, including *Candida* species, should be considered pathogenic. In the future, DNA-techniques, like PCR, could assist in the diagnosis, and might even prove to be more accurate than culturing[8].

Based on our findings, we recommend two-stage revision for all patients with a fungal PJI. There is no evidence that one-stage revision, DAIR or only antifungal therapy have similar results. Based on our findings, we recommend to give systemic antifungal treatment at least until there is absence of clinical signs of infectious symptoms, and normalized infection parameters in blood. Hereinafter, reimplantation can be considered/performed. There is no sufficient evidence that the use of local antifungal treatment has additional benefits. Systemic and local antibacterial drugs should be added (to the cement) when bacterial co-infection is present.

OUTCOMES AFTER
OF PERIPROSTHETIC JOINT INFECTIONS

CHAPTER **11**

Quality of life after staged revision for infected total hip arthroplasty

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CHAPTER 11

Quality of life after staged revision for infected total hip arthroplasty

Abstract

The aim of this review was to assess (health-related) quality of life ([HR]QoL) after one-stage or two-stage revision for periprosthetic joint infection of the hip (PJI). Additionally, we compared (HR)QoL scores with normative population scores to assess whether QoL is reduced after revision for PJI.

A systematic search was performed in Embase, Cochrane and PubMed. We included articles that reported (HR)QoL questionnaires after staged revision for hip PJI with a minimum follow-up of 24 months. Methodological quality was assessed using the MINORS (Methodological Index for NOn-Randomized Studies) score.

The search produced 11,195 results. We selected 12 papers describing two-stage revisions. The mean MINORS score was 9.8. Average WOMAC scores of 185 patients with a mean follow-up of 69.8 months were 73. Average Short Form 36 (SF-36) scores of 159 patients with a mean follow-up of 40.7 months were 40.4 for the physical component score (PCS) and 51.6 for the mental component score (MCS). Average Short Form 12 (SF-12) scores of 154 patients with a mean follow-up of 73.4 months were: a PCS of 35.4 and a MCS of 49.1. The WOMAC, SF-12 (PCS) and SF-36 (PCS) were respectively 12%, 26.7% and 14.8% lower, compared to normative values.

Patients who underwent two-stage revision for hip PJI had substantially lower (physical component) (HR)QoL scores, but mental scores were comparable to the general population.

Introduction

In patients with degenerative disease of the hip, total hip arthroplasty (THA) is a frequently performed orthopedic procedure that improves quality of life (QoL)[309–311]. QoL is an abstract and broad concept, commonly described as the patients' own appreciation of physical, mental and social well-being. Health related quality of life (HRQoL) is a narrow concept, which describes the domains of quality of life influenced by health status and problems[312]. QoL may be affected if complications occur, such as recurrent dislocations and aseptic loosening. One of the most severe complications after THA is periprosthetic joint infection (PJI). Surgical and long-term antibiotic treatment, that are needed to eradicate infection, debilitate patients and may cause long term impairments.

PJI can be classified, according to duration and onset of symptoms, as acute, chronic or hematogenous[8]. When PJI exists for at least 3 weeks or when PJI occurs longer than 30 days after prosthesis placement, either one-stage or two-stage revision is recommended[8]. Two-stage revision is most commonly performed; onestage revision is an alternative in selected patients, with a known pathogen and good soft tissue envelope,

and is assumed to be less debilitating. For acute PJI, debridement, antibiotics, irrigation and implant retention (DAIR) is considered the optimal treatment method[27]. Staged revision for PJI requires surgery and several weeks of intravenous antibiotic agents; therefore, it is likely that patients' (HR)QoL is severely affected. The most common method of measuring QoL and HRQoL is with questionnaires. Table 1 demonstrates an overview of validated (HR)QoL questionnaires. For patients who have had an aseptic hip revision, a decrease in QoL has been described[313,314]. One might expect that (HR)QoL would decrease even more after a septic hip revision. However, the available literature is hard to interpret and to compare, because of the multiple questionnaires, with multiple subscales, that are used to assess (HR)QoL, and different methods of reporting results (among others absolute scores versus relative scores between 0 and 100).
To our knowledge there is no systematic summary of quality-of-life outcomes after staged revision for PJI. The aim of this systematic review is therefore to summarize QoL and HRQoL outcomes after one-stage and two-stage revision for hip PJI. Specific purposes were to report (HR)QoL scores, derived from the questionnaires reported in Table 1, and to report differences between these scores and norm values, based on general populations. With this review we hope to provide more insight in the long-term effects of staged revisions for PJI of the hip.

Name	Domain	Aim	Questions (n)	Subscales / Domains	
Short Form 36 (**SF-36**)[18]	QoL	General health	36	**Physical Component Score (PCS):** Physical functioning Bodily pain Physical role functioning General health perceptions	**Mental Component Score (MCS):** Vitality Social role functioning Mental health Emotional role functioning
Short Form 12 (**SF-12**)[11]	QoL	General health	12	**Physical Component Score (PCS):** Physical functioning Bodily pain Physical role functioning General health perceptions	**Mental Component Score (MCS):** Vitality Social role functioning Mental health Emotional role functioning
EuroQol-5D (**EQ-5D**)[14]	QoL	General health	6	Pain 1, Mobility 1, Activities 1, Pain 1, Anxiety/Depression 1	
Hip disability and Osteoarthritis Outcome Score (**HOOS**)[12]	(HR)QoL	Joint (hip) specific	40	Symptoms 3, Stiffness 2, pain 10, Daily activities 10, Sport 4, QoL 4	
Western Ontario and McMasters Universities Osteoarthritis Index (**WOMAC**)[13]	(HR)QoL	Disease (osteoarthritis) specific	24	Pain 5, Function 17, Stiffness 5	

Table 1: Overview of (Health Related) (HR) Quality of Life (QoL) questionnaires.

Methods

A computerized systematic search was conducted in PubMed (1966 to April 2015), Embase (1946 to April 2015) and the Cochrane library (April 2015). This review was conducted using the PRISMA statement[95]. The following key words and medical subject headings were used: Arthroplasty, 'Replacement, joint" [Mesh], "prosthetic joint", ar-

throplast* (truncated), prostheses* (truncated), replacement, hip, joint, septic, infection, infectious, “Prosthesis-Related Infections” [Mesh]. The institutions clinical librarian was consulted for support with the search. Citations were independently screened by three reviewers (LR, JK, SC). Reference lists of the selected articles were checked manually to retrieve publications not found in the systematic search. Search results were reviewed by title and abstract and studies were included if they met the following inclusion criteria:

- Patients treated with one- or two-stage revision THA after infected primary THA, revision THA, hemi-arthroplasty, or osteosynthesis of the hip;
- A minimum follow-up of 24 months;
- A minimum of 10 patients;
- QoL or HRQoL measured with a validated questionnaire (Table 1);
- And separate outcome scores for THA have to be reported if multiple joints were studied.

Two reviewers (LR, JK) independently assessed the methodological quality of the selected articles, by using the MINORS (Methodological Index for NOn-Randomized Studies) standardized checklist for non-randomized studies[315]. This checklist contains 8 items for non-comparative studies and an additional four questions for comparative studies. For each item a score of 0, 1 or 2 can be given, which means that a maximum score of 16 can be reached for non-comparative studies and a maximum score of 24 for comparative studies. Disagreements were discussed during a consensus meeting.

Data extraction

Data was extracted from the selected studies, regarding study design, type of treatment, number of patients who were free of infection after treatment, number of patients available at follow-up, mean length of follow-up and outcome questionnaires (including range or SD when available). Treatment success was defined as absence of PJI symptoms without chronic suppressive antibiotic use at the last moment of follow-up. Patients who were deceased unrelated to infection at time of follow-up were not defined as failures.

Analysis

The selected studies were organized in groups by type of (HR)QoL questionnaire: the Short Form 36 (SF-36), the Short Form 12 (SF-12), the Western Ontario and McMaster Universities Arthritis Index (WOMAC), EuroQol 5D (EQ-5D) and the Hip disability and Osteoarthritis Outcome Score (HOOS)[316–318]. The WOMAC was converted to a 100-point scale, 0 being poor and 100 being the best possible outcome. For studies that only reported individual components, a total score was calculated from the pain stiffness and function subscales. The Short Form 36 (SF- 36) and Short Form 12 (SF-12) were converted to a physical component score (PCS) and mental component score (MCS)[319]. These conversions made it possible to calculate weighted averages, based on the number of participants in each study, which was done for each questionnaire separately. To

evaluate these scores a comparison was made between these average scores and norm values for a healthy population. For the WOMAC score a normative value of 82.9 was taken, which is the average WOMAC score for a general (Canadian) population (aged 60-64)[320]. For the SF-12, a score of 48.3 was taken for the PCS subscale and a score of 52.8 for the MCS subscale as reference values, which is based on a general Dutch population (aged 55-65)[321,322]. The reference values used for the SF-36 scores were 47.4 and 51.7 for the PCS and the MCS respectively, based on a general American population (aged 55-64)[323]. Normative values for the HOOS questionnaire could not be found.

Results

The systematic search resulted in a total of 11195 articles (PubMed, Embase), of which 232 abstracts of articles that potentially met the inclusion criteria were assessed. After reviewing the abstracts and reference checking, a selection of 18 full-text papers was made, which were fully read. The article selection process is described in Figure 1. Six papers did not meet the inclusion criteria and were excluded. Two of these selected studies solely focused on QoL during the two-stage treatment interval[9,10], one did not use a validated (HR)QoL outcome measure[324], one described QoL after DAIR treatment[39], and two did not differentiate between different joints and type of treatment[39,325]. Twelve studies describing (HR)QoL after two-stage revision for hip PJI were included[304,326,335,336,327–334]. None of these studies evaluated (HR)QoL after one-stage revision. An overview of all selected studies is presented in Table 2.

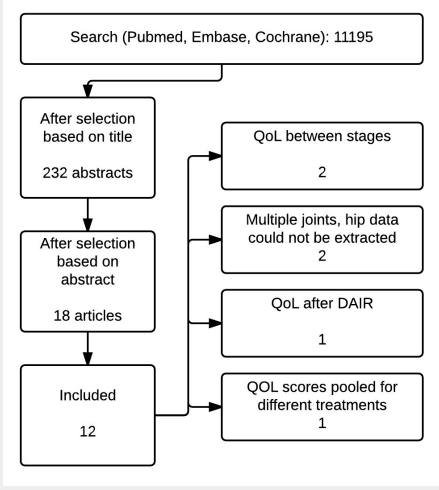


Figure 1: Search and article selection process flowchart; QoL: quality of life; DAIR: debridement, antibiotics, irrigation and implant retention.

Methodological quality

Table 3 describes MINORS criteria scores for each study. The mean MINORS score was 9.8, indicating moderate study quality. There was a great variety in study design, which is described in Table 2. The study by Barbaric *et al.* had the lowest methodological quality, resulting in a MINORS score of 5[336]. The study did not provide an objective study endpoint, due to a heterogeneous study group and inadequate reporting of questionnaires. Eleven studies described a sufficient follow-up of at least 2 years. The mean loss to follow-up was 25.2% (range 0% – 57%).
Different methods of describing questionnaire outcomes were used.

Some articles reported total scores where others only used sub-scores. There was also great variability in the reporting of absolute scores versus relative scores between 0 and 100. Five studies provided a standard deviation (SD) when describing (HR)QoL[326,329–331,335]. Six articles described which statistical test was used and described when results were considered significant[329,331–335].

Questionnaires and outcome groups

The WOMAC, SF-12, SF-36 and HOOS questionnaires were used to report (HR)QoL. None of these studies used the EQ-5D to report QoL. Most studies subdivided the study cohort in outcome groups and reported outcomes for (HR)QoL for these groups separately. These outcome groups are described in Table 2.

WOMAC

Seven studies used the WOMAC score. Of these studies, mean age was 63.7 years. A total of 282 patients were treated with a two-stage revision, of whom 257 (91%) were successfully treated. At a mean follow-up of 69.8 months (range 40-144), 185 (65%) patients were available for assessment. The weighted mean total WOMAC score was 73.1. In Table 4, an overview of the response rates and WOMAC scores for each study can be seen. The mean score was 12% lower, compared to the norm value of 82.9.

SF-36

Four papers reported SF-36 scores. Of these studies, the mean age was 66.1 years. A total of 195 patients were treated, of whom 169 (87%) were free of infection after treatment. 159 (81%) patients filled out questionnaires, at a mean follow-up of 40.7 months (range 32-48). The weighted mean PCS score was 40.4 and mean MCS was 51.6. SF-36 scores and response rates are presented in Table 5. The PCS score was 14.8% lower compared to the norm value of 47.4. The MCS was 0.2% lower (norm value 51.7).

SF-12

Five studies used the SF-12 questionnaire. Of these studies, the mean age was 67.3. There were 269 patients, of whom 238 patients had a successful treatment outcome (88%). At a mean follow-up of 73.4 months (range 40-144), 154 patients (57%) responded. The weighted mean PCS score was 35.4 and the mean MCS was 49.1. SF-12 scores are presented in Table 6. The score was 26.7% lower compared to the norm value of PCS 48.3, and 2.3% lower for the MCS (52.8).

HOOS

Van Diemen *et al*. reported the HOOS on 136 patients with a mean age of 64.4. There were 118 patients (86%) with successful treatment. Of the successfully treated patients, the mean HOOS score was 54, after a mean of 99.6 months[304].

Author	Year	Description	Control group	Questionnaires	Outcome group
van Diemen	2013	Follow-up on 136 infected THA	-	HOOS	2
Parvizi	2008	Prospective cohort two-stage revisions.	-	SF-36	1
Biring	2009	Two-stage revision with Prostalac spacer.	-	SF-12, WOMAC	1
Romano	2010	Septic vs. aseptic revision	Aseptic revisions (n=40)	SF-12, WOMAC	1
Hsieh	2004	Two-stage revisions with custom made spacer.	-	WOMAC	2
Masri	2007	Cementless two-stage revision	-	WOMAC	2
Kappler	2012	Infections after hip osteosynthesis	-	SF-12, WOMAC	3
Leung	2011	Two-stage revision after MRSA PJI	-	SF-12, WOMAC	2
Sabry	2013	Two-stage revision with custom made vs. commercially available spacers	commercially available (n=27) custom made (n=51)	SF-12	1
Barbaric	2014	Patient satisfaction after revision and resection arthroplasty	Resection arthroplasty (n=53)	WOMAC, SF-36	4
Boettner	2011	Functional and emotional results with septic and aseptic revision	Aseptic revisions (n=195)	SF-36	2
Younger	1997	Two-stage revision with custom made spacer	-	SF-36	1

Table 2: Overview of selected studies; THA: total hip arthroplasty; MRSA: methicillin resistant Staphylococcus aureus; PJI: periprosthetic joint infection; HOOS: Hip disability and Osteoarthritis Outcome Score; SF-36: Short Form 36; SF-12: Short Form 12; WOMAC: Western Ontario and McMasters Universities Osteoarthritis Index. Outcome groups: 1: regardless of treatment success or re-revision; 2: free of infection without re-revisions; 3: free of infection with re-revisions; 4: unclear.

Author	Year	1.	2.	3.	4.	5.	6.	7.	8.	9.	10.	11.	12.	Total:
van Diemen	2013	2	0	0	2	0	2	1	0					**7**
Parvizi	2008	2	2	0	2	0	2	1	0					**9**
Biring	2009	2	2	0	2	0	2	1	0					**9**
Romano	2010	2	2	2	2	0	2	2	2	2	2	1	1	**20**
Hsieh	2004	1	2	2	2	0	2	1	0					**10**
Masri	2007	2	2	0	2	0	2	1	0					**9**
Kappler	2012	1	2	0	2	0	1	1	0					**7**
Leung	2011	2	2	0	2	0	2	1	0					**9**
Sabry	2013	2	2	0	2	2	2	0	0	2	1	0	2	**15**
Barbaric	2014	1	0	0	1	0	0	1	0	1	0	1	0	**5**
Boettner	2011	2	2	0	2	0	2	1	0	2	2	1	1	**15**
Younger	1997	2	2	0	2	0	2	2	0					**10**

Table 3: MINORS (Methodological Index for NOn-Randomized Studies) score for each study; 1: a clearly stated aim; 2: inclusion of consecutive patients; 3: prospective collection of data; 4: endpoints appropriate to the aim of the study; 5: unbiased assessment of the study endpoint; 6: follow-up period appropriate to the aim of the study; 7: loss to follow-up less than 5%; 8: prospective calculation of the study size.
For comparative studies: 9: an adequate control group; 10: contemporary groups; 11: baseline equivalence of groups; 12: adequate statistical analyses

Author	Year	Design	Age	Treatment	Nr. Tr.	Nr. Suc.	Success %	FU (Months)	FU Nr.	FU %	WOMAC Pain	WOMAC Stiffness	WOMAC Function	WOMAC total
Barbaric	2014	Retro	64	Two-stage revision	20	20	100%	Not mentioned	17	85%				74
Biring	2009	Retro	64	Two-stage revision	99	88	89%	144 (120-180)	34	34%	89.3	89	76	80.6
Romano	2010	Pro	65	Two-stage revision	40	39	98%	48 (24-72)	39	98%	77.4 (22.8)	71.4 (24.1)	76.6 (21.3)	76
Hsieh	2004	Pro	61	Two-stage revision	42	40	95%	55,2 (36-66)	33	79%	88.2 (20.7)	72.1 (25.6)	85.3 (19.6)	84.8
Masri	2007	Retro	65	Two-stage revision	29	26	90%	47 (22-88)	26	90%				54.0
Kappler	2012	Retro	63	Two-stage revision	14	14	100%	40 (4-100)	9	64%				78
Leung	2011	Retro	64	Two-stage revision	38	30	79%	58 (24-123)	27	71%	67.1	64.3	59.5	62
Summary	-	-	**63.7***	-	**282**	**257**	**91%**	**69.8***	**185**	**65%**				**73.1***

Table 4: Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) scores; Nr: number; Tr: treated; Suc: successfully treated; FU: follow-up; Retro: retrospective; Pro: prospective; *=weighted mean.

Author	Year	Design	Age	Treatment	Nr. Treated	Nr. Success	Success %	FU (months)	FU nr.	FU %	PCS	MCS
Barbaric	2014	Retrospective	64	Two-stage revision	20	20	100%	Not mentioned	17	85%	36.5	48.5
Parvizi	2008	Retrospective	65	Two-stage revision	54	40	74%	32 (24-76)	49	91%	48.0	60.0
Boettner	2011	Retrospective	67	Two-stage revision	73	64	88%	48 (24-112)	45	62%	36.0	45.0
Younger	1997	Retrospective	67	Two-stage revision	48	45	94%	43 (24-63)	48	100%	38.0	50.4
Summary	-	-	**66.1***	-	**195**	**169**	**87%**	**40.7***	**159**	**81%**	**40.4***	**51.6***

Table 5: Short Form 36 (SF-36) scores; FU: follow-up; PCS: physical component score; MCS: mental component score; * =weighted mean.

Author	Year	Design	Age	Treatment	Nr. Treated	Nr. Success	Success %	FU Months	Nr. FU	FU %	PCS	MCS
Romano	2010	Prospective	65.3	Two-stage revision	40	39	98%	48(24-72)	39	98%	35.6 (12.4)	43.1 (13.8)
Kappler	2012	Retrospective	63	Two-stage revision	14	14	100%	40(4-100)	9	64%	35	54.0
Sabry	2013	Retrospective	63.8	Two-stage revision	78	67	86%	58(24-153)	45	58%	38.9	50.9
Biring	2009	Retrospective	72	Two-stage revision	99	88	89%	144(120-180)	34	34%	33.5	53.1
Leung	2011	Retrospective	63.5	Two-stage revision	38	30	79%	58(24-123)	27	71%	32.4	47.9
Summary			**67.3***		**269**	**238**	**88%**	**73.4***	**154**	**57%**	**35.4***	**49.1***

Table 6: Short Form 12 (SF-12) scores; FU: follow-up; PCS: physical component score; MCS: mental component score; * =weighted mean.

Discussion

The aim of this systematic review was to evaluate (HR)QoL scores after staged revision for PJI. This study demonstrated that results for the WOMAC, SF-12 (PCS) and SF-36 (PCS) were respectively 12%, 26.7% and 14.8% lower compared to norm values, collected among the general population with comparable age[320,321,323]. These results imply that patients who underwent a two-stage revision scored lower than the general population on physical aspects of QoL. However, the mental aspects of QoL were rated relatively high by these patients, concerning the scores on the MCS subscale of

the SF-12 and SF-36 (2.3% and 0.3% lower compared to the general population). The quality of the selected studies was moderate due to their retrospective design, inconsistent composition of outcome groups and lack of a power analysis. None of the selected studies described (HR)QoL after one-stage revision.

Our results show a mean weighted total WOMAC score of 73.1. This is similar to previous studies on aseptic revisions, in which WOMAC scores ranged from 63 to 74.5 in large groups of patients (n >45) with at least 2 years of follow-up[313,314,337]. One of the selected studies in this review even demonstrates a higher WOMAC function subscale after two-stage revision compared to aseptic revision[331]. In line with these results, one of the comparative studies in our review reported superior SF-36 physical functioning and role physical sub scores after septic two-stage revision compared to aseptic revisions[332]. This indicates that an interval with a resection arthroplasty and two surgical interventions may not negatively influence (HR)QoL, compared to aseptic revision arthroplasty of the hip.

We have only focused on long term (HR)QoL scores after two-stage PJI revision and could not report the results of one-stage revisions due to the lack of studies reporting the (HR)QoL after septic one-stage THA revisions. To conclude whether a two-stage revision should be preferred to a one-stage revision, it is interesting to look at the QoL during the interval between the stages in two-stage revision. Two studies that focused on QoL in the interval between two-stages measured the SF-36. Scharfenberger *et al*. report a PCS of 32 and an MCS of 48 during a mean interval of 13.2 months, and Peng *et al*. found a PCS of 38.8 and an MCS of 37.1 during a mean interval of 7.2 months[9,10]. Both studies used an articulating antibiotic loaded spacer. The PCS during the interval between resection arthroplasty and definitive arthroplasty were 8.6 and 15.4 points lower compared to the normative values, and 1.6 and 8.4 points lower compared to values for definitive arthroplasty after hip PJI, we have found in this review. The MCS during the interval between resection arthroplasty and definitive arthroplasty were 3.6 and 14.6 points lower compared to the normative values, and 3.6 and 14.5 points lower compared to the results after two-stage revision, reported in this review. These relatively low QoL scores found in the interval might be a reason to prefer one-stage revision over twostage revision. This should be in line with the conclusion drawn in the study of Bedair *et al*., who have used a mathematical decision analysis tool to evaluate the best treatment for PJI using HRQoL as the primary outcome[338]. This study favored one-stage revision and concluded that the success rate of one-stage revision has to be below 66%, before two-stage exchange would lead to a better HRQoL. Nevertheless, this model did not include actual patient data.

This systematic review has several limitations. Studies that were included had variable MINORS scores and showed a corresponding variability in quality. In general, the quality of the statistical analyses was low, and in seven studies these analyses were even lacking[304,326–328,330,336]. No unambiguous definition of PJI or treatment success was seen in the group as a whole. This might be a reason for the heterogeneous outcome groups we have found for all questionnaires (reported in Table 2). In line with results reported by Woolacott *et al*., a large variability was seen in means of the reported WOMAC scores[339]. This seems to be caused by the lack of accordance in presenting total WOMAC scores,

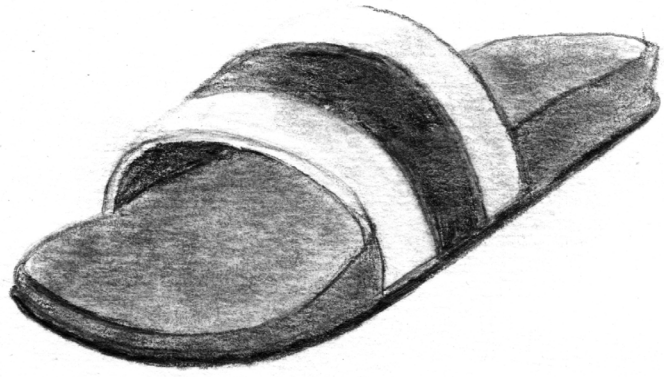
or WOMAC scores on subscales separately. Exclusive use of a total WOMAC score may cause an underrepresentation of differences in pain, stiffness or function subscales between different studies[339].With the SF-12 and SF-36, a similar underrepresentation of differences in subscales may occur[340]. Most of the included studies were retrospective of nature, and groups were relatively small. As a result of the small groups and heterogeneity, a relatively wide range of scores is seen. We corrected for smaller groups by calculating weighted averages.

Based on this systematic review, we can conclude that the number of studies that have reported HRQoL after PJI is low, and the methodological quality of studies is variable. Nevertheless, this review has revealed that patients who underwent two-stage revision for hip PJI have lower HRQoL scores and lower PCS QoL scores than the general population. This confirms poorer outcome of two-stage revision. Surprisingly, there was only a minimal difference with HRQoL after aseptic revisions, and the mental component scores of HRQoL were even comparable with scores reported in a general population. Whether QoL after two-stage differs from one-stage revision remains unclear. The comparison of (HR)QoL scores before THA, after THA, during treatment interval and after revision for PJI would be a welcome addition to current knowledge.

OUTCOMES AFTER
OF PERIPROSTHETIC JOINT INFECTIONS

CHAPTER 12

Results and patient reported outcome measures (PROMs) after one-stage revision for periprosthetic joint infection of the hip: a single-center retrospective study



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CHAPTER 12

Results and patient reported outcome measures (PROMs) after one-stage revision for periprosthetic joint infection of the hip: a single-center retrospective study

Abstract

Little is known about functional outcome and quality of life (QoL) after one-stage revision for periprosthetic joint infection (PJI) of the hip.
A cohort of 30 subjects treated with one-stage revision between 2011 and 2015 was identified, and questionnaires on functional outcome and QoL were distributed.
28 subjects were successfully treated (93%). Most subjects were referred from other hospitals. Coagulase-negative *Staphylococcus* was found in 50% of the cases, and 40% of all cultured bacteria were multidrug-resistant. 25% had subsequent revision surgery, unrelated to PJI. Functional outcome was good and QoL scores were high, comparable to prosthetic joint revision surgery in general.
Although the cohort was small and statistical analysis was not performed, this study showed that excellent results can be obtained with one-stage revision for hip PJI. Functional outcome and QoL was comparable to prosthetic joint revision surgery in general.

Introduction

Periprosthetic joint infection (PJI) of the hip is one of the most precarious complications of total hip arthroplasty (THA). It generally requires one or more operations, weeks of hospitalization and long courses of antibiotic treatment. It is a great financial and logistic burden to hospitals and health care in general[8,104]. The patients themselves, however, are the ones most afflicted by the complication. Treatment methods range from life-long suppressive antibiotic therapy (for inoperable patients with a low grade PJI) to months of living without a functioning hip articulation (Girdlestone procedure) and to curative therapy with joint replacement[8]. In joint replacement therapy, two-stage revision is the gold standard. In this procedure, the arthroplasty is resected and reimplantation is performed after weeks or months of treatment with antibiotics. A one-stage revision, however, according to guidelines, is the preferred option for non-acute PJI in patients with an adequate soft tissue envelope, sufficient bone stock and a preoperatively identified non-resistant microorganism[8].

In one-stage revision, all arthroplasty components are removed, including any polymethylmethacrylate (PMMA) bone cement, thorough surgical debridement and extensive irrigation are performed, after which new arthroplasty components are directly reimplanted. Rigorous removal of all possibly contaminated tissue and foreign body material is paramount for infection eradication[8,341]. Success rates of one-stage revision in different studies vary between 76 and 100%, but in patients with favorable circumstances (e.g. infection with non-resistant microorganism, adequate soft tissue) lie around 90%[8,342]. A recent systematic review suggested that one-stage revision may be

comparable to two-stage revision in terms of reinfection risk[341].

Studies on functional outcomes after one-stage revision are scarce, and only one found better functional outcomes compared to two-stage revision (Harris Hip Score and Visual Analogue Scale for pain)[343]. To our knowledge, no published studies have described the effect of one-stage revision on the quality of life (QoL) of patients[11]. However, a trial protocol has been published on one-stage versus two-stage revisions, including QoL and functional outcome at follow-up, but these results have not been published yet[344].

The aim of this study is to describe the outcomes of a retrospectively selected cohort after one-stage revision for hip PJI, in terms of reinfection rate, functional scores and quality of life.

Methods

Subject selection and inclusion

We searched our hospital's database of performed surgical procedures for all ICPC (International Classification of Primary Care) and surgery codes possibly linked to PJI procedures, to find patients who were surgically treated for hip PJI between January 2011 and December 2015. Electronic patient records were retrospectively analyzed and relevant data were extracted.

Subjects were included if they underwent one-stage revision for PJI of THA in the study period. Excluded were subjects with PJI of a hemi-arthroplasty, incomplete removal of foreign body material (i.e., arthroplasty components or bone cement) and subjects in whom PJI criteria were not met. PJI criteria were: two or more positive periprosthetic cultures with phenotypically identical organisms, or a sinus tract communicating with the joint, or having at least three of the following minor criteria: elevated serum C-reactive protein (CRP) AND erythrocyte sedimentation rate (ESR); elevated synovial fluid white blood cell (WBC) count OR ++ result on leukocyte esterase test strip; elevated synovial fluid polymorphonuclear neutrophil percentage (PMN%); positive histological analysis of periprosthetic tissue; a single positive culture[18]. If subjects died within a year of follow-up, unrelated to PJI, success was defined as 'uncertain', and subjects were excluded. A minimal follow-up of one year was required in all other cases.

Informed consent and ethical approval

Ethical approval for this study was received from the ethical committee of our hospital, with approval number 2017.181. Data collection and subject contacts were handled according to the ethical standards in the 1964 Declaration of Helsinki.

Subjects meeting our inclusion criteria were informed about the proposed study by letter and invited to participate. Instructions and information about the study were included, along with the questionnaires and reply envelope. If no reply was received, subjects were contacted by telephone.

Treatment

In our institution, one-stage revision for PJI is performed by one orthopedic surgeon, the senior author (RS), and is the treatment method for all patients with hip PJI for chronic infection or when a sinus tract is present. Two-stage revision is only performed when patients have sepsis or are otherwise severely immunocompromised (e.g., undergoing chemotherapy treatment), or when bone defects are so extensive that a tumor prosthesis is necessary. This is a protocol that is not generally performed in other Dutch hospitals, where one-stage revision is much less performed.

All hips were revised using a posterolateral approach in lateral decubitus position. Surgery was performed under strict sterile conditions. After removal of all arthroplasty components, complete PMMA bone cement removal (if present), thorough debridement and irrigation with at least 6L of saline, reimplantation was performed in the same session. Choice of THA model and use of (gentamicin loaded) bone cement was based on bone stock and quality, whether a fracture had occurred and whether osteotomy was required for THA removal. In most cases an uncemented primary or modular stem was used, and the acetabular component was also uncemented in the majority of cases.

If subjects were not already receiving antibiotics aimed at pathogens from culture results prior to surgery, they received intravenous vancomycin (1000 milligrams twice daily, adjusted to renal function and serum levels) and ciprofloxacin (400 milligrams three times daily, or adjusted to renal function) after all cultures were taken. Postoperative antibiotic therapy, based on bacterial susceptibility (according to the European Committee on Antimicrobial Susceptibility Testing (EUCAST) definitions) and in consultation with an infectious diseases specialist and a medical microbiologist, was administered for a minimum of 6 weeks, the standard duration being 3 months, but ultimate therapy duration depended on an individual subject's parameters e.g. presence of clinical and laboratory signs of inflammation and tolerance of therapy. Intravenous therapy was usually given for two weeks, followed by oral antibiotic therapy when agents with a high bioavailability were available e.g., rifampicin and quinolones. In subjects where such antibiotics could not be given, due to inherent or acquired antimicrobial resistance or allergies, outpatient parenteral antibiotic therapy was given.

Outcome

Successful outcome was defined as retainment of THA after one-stage revision, without any subsequent surgical procedures for PJI (debridement, antibiotics, irrigation and implant retention (DAIR), one-stage or two-stage revision or arthroplasty removal), without the chronic use of antimicrobial agents, and without signs or symptoms of PJI at follow-up. If other surgical procedures were performed, patient records were checked: if the surgical report, postoperative notes or culture results suggested PJI relapse, this was defined as treatment failure. Otherwise, this was noted as 'revision for other reason', and treatment was regarded successful. In patient records, culture results were checked and infections were classified as whether or not being polymicrobial PJI and culture negative PJI, and microorganisms were categorized as non-resistant or multidrug-resistant according to standard definitions[345].

If subjects died as a result of PJI, this was defined as failure. As mentioned above, if subjects died within a year of follow-up, unrelated to PJI, success was defined as 'uncertain', and subjects were excluded. If subjects died after more than a year of follow-up, unrelated to PJI, and without subsequent procedures related to PJI, treatment was considered successful.

Questionnaires

For measurement of outcome, three questionnaires were used, according to the advice of the Dutch Orthopedic Society (Nederlandse Orthopaedische Vereniging, NOV)[346]: Oxford Hip Score (OHS, score range 0 to 48), Hip disability and Osteoarthritis Outcome Score (HOOS, score range 0-100) and EuroQol five dimensions questionnaire (EQ-5D, score range -0.329 to 1). All three have validated Dutch translations[347–349]. Furthermore, Visual Analogue Score (VAS) pain for current pain (100-0), VAS satisfaction for overall satisfaction after one-stage revision (0-100) and a question whether the subject had been treated elsewhere for the same hip after the one-stage revision, were added.

Results

In the study period, 79 subjects were treated for PJI of the hip. One subject died within a year (after 3 weeks, unrelated to PJI), and treatment success was therefore classified as 'uncertain'. This subject was removed from further analysis. Of the remaining subjects, 30 met the inclusion criteria (Figure 1). Of these 30, two subjects underwent subsequent surgical procedures related to PJI after one-stage revision, and were therefore classified as treatment failure (one subject underwent DAIR twice after one-stage revision, and one subject underwent DAIR and a subsequent Girdlestone procedure after one-stage revision). 28 Subjects were treated successfully (93%). Because only two cases were categorized as treatment failure, no statistical analysis was performed on the data.

All patients received 6-12 weeks of antibiotic treatment. The mean follow-up was more than 3 years. During the follow-up, five subjects died, of which one in the failure group (unrelated to PJI, but underwent two subsequent DAIR procedures). For subject characteristics, see Table 1. For a list of subjects and their positive PJI criteria, see Table 2.

Most subjects were patients referred from other hospitals (60%). A sinus tract was present in 37% of all subjects. In 23 cases, the causative microorganism was known preoperatively (77%), either from aspiration or positive blood culture results.
In 50% of all cases, coagulase-negative *Staphylococci* were found. 40% of all cultured bacteria were multidrug-resistant to antibiotic agents (all in the failure group). None of the multidrug-resistant microorganisms were resistant to vancomycin, when vancomycin susceptibility was tested. No methicillin resistant *Staphylococcus aureus* (MRSA) was cultured. 23% subjects had a polymicrobial PJI. In two cases (6%), cultures remained negative.

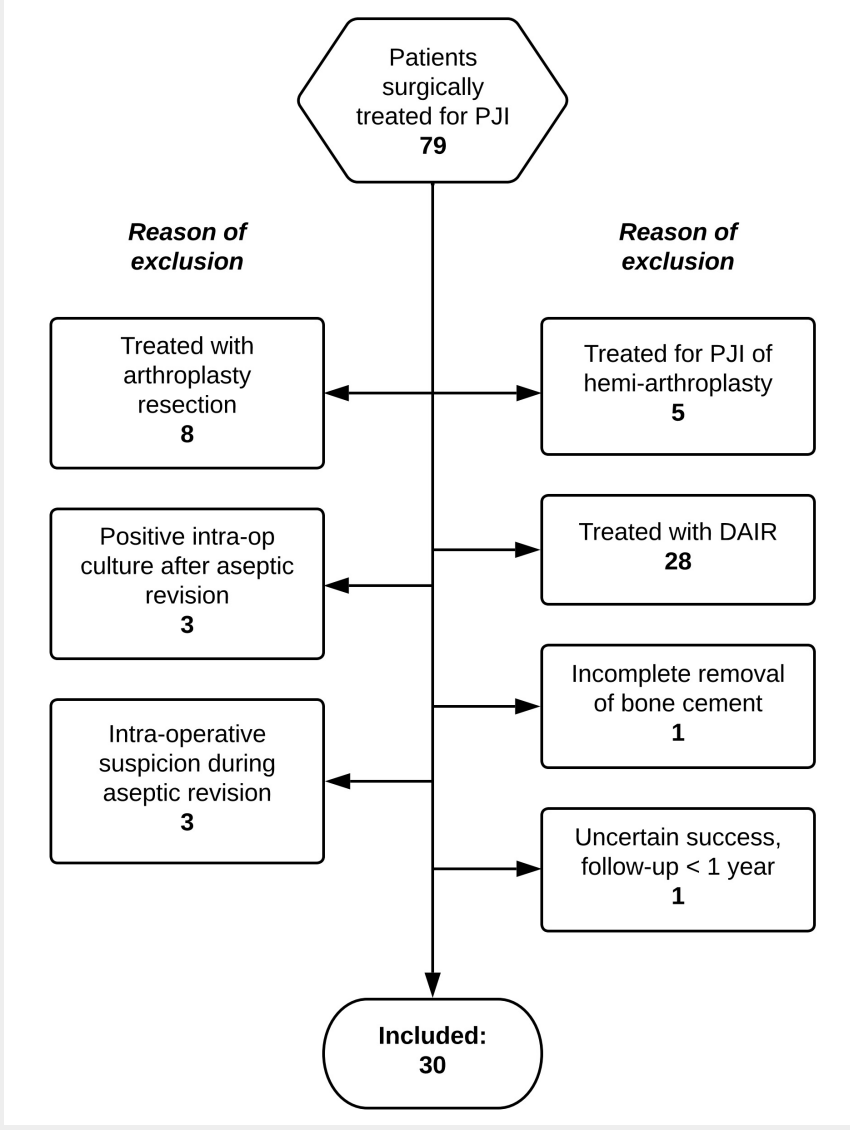

Figure 1: Flowchart of subject inclusion with numbers; PJI: periprosthetic joint infection; DAIR: debridement, antibiotics, irrigation and implant retention.

	Total	Success	Failure
Number of subjects	30	28	2
Mean age in years (SD)	71.8 (10.2)	71.0 (10.1)	82.1 (6.1)
Mean follow-up in months (SD)	39.8 (19.8)	41.3 (19.3)	18.7 (17.7)
Male: female (% male)	9:21 (43)	9:19 (47)	0:2 (0)
Deceased (%)	5 (17)	4 (14)	1
ASA classification			
I	4	4	0
II	11	11	0
III	14	12	2
IV	1	1	0
V	0	0	0
Current smoker (%)	6 (20)	6 (21)	0
Body mass index (SD)	28.8 (6.4)	28.8 (6.0)	29.0 (14.3)
Body mass index > 30 kg/m2 (%)	11 (37)	10 (36)	1**
Body mass index > 35 kg/m2 (%)	6 (20)	5 (18)	1**
Co-morbidities*			
Cardiovascular (%)	18 (60)	17 (61)	1
Pulmonary (%)	8 (27)	8 (29)	0
Renal failure (%)	2 (7)	2 (7)	0
Diabetes mellitus (%)	3 (10)	3 (11)	0

Table 1: Subject characteristics; ASA: American Society of Anesthesiologists Score; SD: standard deviation; *subjects were considered to have a comorbidity if it was described in the subject's medical records or if the subject used medication for the comorbidity; **both are the same patient, with a body mass index of 39.

The average duration of surgery was 182 minutes. Bone allograft was used in three cases (10%), of which two cases of failure. Femoral osteotomy was performed in 40% (n=12), and intraoperative fractures occurred in 13% (n=4). For subjects with treatment failure, surgery time was longer than for subjects with treatment success, as well as more frequent use of allograft bone, more frequently performed femoral osteotomy and occurrence of fractures. Reoperations unrelated to PJI were performed in 25% of successfully treated subjects (n=7): of these, revision for recurrent dislocations took place in four cases, one subject was treated for a periprosthetic fracture three months after one-stage revision, removal of osteosynthesis material in one case, and femoral stem revision after stem subsidence occurred in one subject. In all cases, cultures in subsequent procedures were negative.

21 subjects responded to our survey (84% of all living subjects), but some replied only partly. Survey results can be seen in Table 3. For successfully treated subjects, the mean HOOS was 63 (of 100), OHS 35 (of 48), EQ-5D 0.68 (of 1), EQ-5D-VAS 74 (of 100), VAS pain 31 (of 100), and VAS satisfaction 81 (of 100). The only living subject with treatment failure had worse functional and QoL scores, except for VAS pain (0). None of the respondents reported subsequent surgery on the affected hip elsewhere.

Discussion

Of 30 included subjects who underwent one-stage revision, 28 were considered successfully treated (93%), at a mean follow-up of 40 months. In 50% of cases, coagulase-negative *Staphylococcus* was cultured. 84% of the still living subjects

Subject nr.	Major criterion: 2 or more positive cultures (intraoperative)	Major criterion: sinus tract	Minor criterion: one positive culture; aspiration (A) or intraoperative (I)	Minor criterion: elevated serum markers	Minor criterion: histology**	Microorganism
1*	+			+		Coagulase-negative *Staphylococcus*
2*	+			+		*Corynebacterium spp., Enterobacter spp.*
3	+		+ (A)	+		*Salmonella spp.*
4	+			+		Coagulase-negative *Staphylococcus*
5	+		+ (A)	+		*Streptococcus spp.*
6	+			+		*Enterococcus spp.*
7	+			+		*Enterococcus spp.*
8	+		+ (A)	+		*Staphylococcus aureus*
9		+	+ (I)	+		*Enterococcus spp.*
10		+		+	+	-
11	+	+		+		*Enterococcus spp., Morganella spp.*
12	+					Coagulase-negative *Staphylococcus*
13	+	+		+		*Staphylococcus aureus*
14	+			+		Coagulase-negative *Staphylococcus*
15	+			+		*Staphylococcus aureus*
16	+			+		Coagulase-negative *Staphylococcus, Propionibacterium spp.*
17	+	+		+		Coagulase-negative *Staphylococcus*
18		+	+ (A)	+		Coagulase-negative *Staphylococcus, Salmonella spp., Pseudomonas spp, Proteus mirabilis*
19		+	+ (A)	+		Coagulase-negative *Staphylococcus*
20	+		+ (A)			Coagulase-negative *Staphylococcus*
21	+			+		Coagulase-negative *Staphylococcus, Corynebacterium spp., Enterococcus spp.*
22	+			+		*Streptococcus spp.*
23	+			+		*Streptococcus spp., Proteus spp.*, anaerobes (unspecified)
24	+			+		Coagulase-negative *Staphylococcus*
25	+			+		Coagulase-negative *Staphylococcus*
26		+		+		-
27	+			+		Coagulase-negative *Staphylococcus*
28		+		+		Coagulase-negative *Staphylococcus, Propionibacterium spp., Streptococcus spp.*
29	+	+	+ (A)	+		*Staphylococcus aureus*
30	+	+	+ (A)			Coagulase-negative *Staphylococcus*

Table 2: Case characteristics and criteria for confirmation of periprosthetic joint infection, according to definition; *treatment failure; **histology was only performed once; white blood cell count, leukocyte esterase test strip and polymorphonuclear neutrophil percentage were never performed in the study period.

	Total	Success	Failure
HOOS	64 (SD 28, range 15-100, n=21)	63 (SD 29, n=20)	90 (n=1)
OHS	35 (SD 11, range 13-48, n=22)	35 (SD 11, n=21)	24 (n=1)
EQ-5D		0.68 (SD 0.30, n=19)	-
EQ-5D-VAS		74 (SD 20, n=19)	-
VAS pain	30 (SD 34, range 0-100, n=22)	31 (SD 34, n=21)	0 (n=1)
VAS satisfaction	77 (SD 30, range 0-100, n=22)	81 (SD 25, n=21)	0 (n=1)

Table 3: Survey results; worst and best scores respectively: HOOS 0-100; OHS 0-48, EQ-5D 0-1, EQ-5D-VAS 0-100, VAS pain 100-0, VAS satisfaction 0-100; HOOS: Hip disability and Osteoarthritis Outcome Score; OHS: Oxford Hip Score; EQ-5D: EuroQol five dimensions questionnaire; VAS: Visual Analogue Score; SD: standard deviation.

responded to our survey regarding functional outcome and quality of life after one-stage revision for hip PJI.

<u>One-stage revision</u>

One-stage revision is a treatment option in cases of PJI occurring more than 30 days after initial hip arthroplasty, when there is good soft tissue and bone stock, microorganism susceptibility to antibiotic agents is high, and bone grafting is not required[8]. Success rates differ, according to selection criteria and study protocols, but lie between 76 and 100%[342]. See Table 4 for a list of recent and large studies on one-stage revision.

The success rate of 93% that was found in this study is comparable to other studies, in a cohort of subjects with 37% sinus tracts and 10% use of allograft bone. The presence of a sinus tract did not seem to lead to worse outcomes in this cohort, as neither of the two patients with treatment failure initially had a sinus tract. In the Infectious Diseases Society of America (IDSA) guidelines, the presence of a sinus tract is no criterion for the choice between one-stage and two-stage revision, although one-stage revision is not recommended when a sinus tract is present[8].

The use of allograft in one-stage revision may have a greater risk of failure according to guidelines[8]. Although the groups are small, both subjects with treatment failure in this cohort underwent one-stage revision with the use of allograft. However, there are also studies that reported good outcomes of one-stage revisions with the use of allograft bone[350,351].

Furthermore, all (3/3) microorganisms in the failure group were multidrug-resistant. On the other hand, 40% of microorganisms in the successfully treated group were resistant as well, so successful treatment with one-stage revision, when PJI is caused by multidrug-resistant microorganisms, is very well possible. However, it may be safe to say that when multidrug-resistant organisms are cultured and bone defects necessitating allograft reconstruction are present, other treatment options, such as two-stage revision, should seriously be considered.

Functional outcome scores

In this cohort, a HOOS of 63 was found for the successfully treated group. To our knowledge, no studies exist on the HOOS score after one-stage revision or DAIR. We found one study that described a HOOS of 54 after two-stage revision[304]. We found only one other study on HOOS after revision surgery: Mahmoud *et al.* found a HOOS of around 70 after cup revision with metal augmentation in 147 subjects[352].

We found a mean score of 35 for OHS in this cohort. One other study described postoperative OHS after one-stage revision. They found a score of 31, comparable to the 35 in this study[353]. In other settings, an OHS of 36 after DAIR treatment[354], and an OHS of 32 in 1176 hip revisions (for all reasons)[355] were described.

Table 4 summarizes other studies that describe functional outcomes after one-stage revision for hip PJI. Most of those studies report outcome using either the Merle d'Aubigné-Postel functional score (MAP) (range 13.3-15.9) or the Harris Hip Score (HHS) (range 65.4-87.8). For both scores, postoperative results were higher than preoperative results. The results of these scores were comparable to results after both two-stage revision and aseptic revision found in other studies[356].

Oussedik *et al.* found a VAS satisfaction of 86 after one-stage revision, comparable to the 81 in this cohort[343]. This study was one of the four to make a comparison between one-stage and two–stage procedures, but was the only one to find differences in functional scores: VAS satisfaction and HHS after five years were higher after one-stage than after two-stage revision (86 versus 69 and 87.8 versus 75.5, respectively)[208,343,357,358].

Functional scores between stages in two-stage revision for hip PJI have been reported by Scharfenberger *et al.*[9]. The mean HHS of 54.5 in the interval with a spacer they reported is lower than the HHS after one-stage revision or after aseptic revision. Furthermore, they reported that 56% of patients were bound to ambulation in their own house.

So, in terms of functional scores, this is the first study to describe HOOS after one-stage revision, and OHS was comparable to one other study on one-stage revision. For both scores, and for other scores described by others, functional outcome of one-stage revision is comparable to aseptic hip revision. Comparison to two-stage revision shows better outcome after one-stage revision in only one of four studies, but functionality in the interval between stages is lower. Larger and better designed comparable studies are necessary for better comparison.

Quality of life

The EQ-5D in this cohort was 0.68, and EQ-5D-VAS was 74. In a recent systematic review on QoL after hip PJI treatment, no studies were found on the effect of one-stage revision on quality of life[11].

Also, no other studies on hip PJI were found that used EQ-5D for assessing QoL. However, after prosthetic joint revision surgery in general, two studies found EQ-5D scores of 0.69 and 0.62, of which Raman *et al.* found an EQ-5D-VAS of 79[359,360]. These results are similar to the EQ-5D scores found in this study. Both Dawson *et al.* and Mahmoud *et al.* found a significant improvement in QoL scores after hip revision

Author	Year	Country	N	Success rate	Duration of antibiotic treatment	Functional scores*	QoL scores	Follow-up
	Studies on one-stage only *(recent studies with >20 cases, all studies with >100 cases)*							
Buchholz	1981	Germany	583	77%	None	-	-	at least 1.5 years
Raut	1995	UK	183	84%	6-12 weeks	Preop MAP (9.8) Postop MAP (14.8)	-	93 months
Wrobleski	1986	UK	102	88%	up to 6 weeks	-	-	38 months
Vielpeau	2002	France	127	88%	unclear	-	-	36 months
Zeller	2014	France	157	94%	12 weeks	-	-	42 months
Ilchmann	2016	Switzerland	39	100%	3 months	Postop HHS (81)	-	6.6 years
Jenny	2014	France	65	83%	9 weeks (range 0-17)	Preop MAP (9.5) Postop MAP (13.3) Postop OHS (31.0)	-	37 months
Whiteside	2017	USA	21	95%	6 weeks (intra-articular)	-	-	63 months
Winkler	2008	Austria	37	92%	2 weeks iv, oral not mentioned	-	-	4.4 years
Hansen	2013	USA/UK	27	70%	minimum 6 weeks	-	-	50 months
Bori	2014	Spain	24	96%	not standard, mean 60 days	Postop MAP (13.8) Postop HHS (65.4)	-	45 months
Rudelli	2008		32	94%	6 months	Preop MAP (7.0) Postop MAP (15.9)	-	103 months
	Studies comparing one- and two-stage; results of one-stage group *(recent studies with >10 cases, all studies with >100 cases)*							
Choi	2013	USA	17	82%	6 weeks	Postop HHS (77) Postop UCLA (4.0)	-	62 months
Klouche	2012	France	38	100%	3 months	Preop MAP (11.1) Postop MAP (15.5)	-	35 months
Oussedik	2010	UK	11	100%	minimum 6 weeks	Preop HHS (40.5) Postop HHS (87.8, higher than two-stage) Postop VAS satisfaction (86, higher than two-stage)	-	6.8 years
De Man	2011	Switzerland	22	95%	8-12 weeks	Postop HHS (84)	-	3.8 years

Table 4: Overview of studies on one-stage revision; QoL: quality of life; MAP: Merle d'Aubigné-Postel; HHS: Harris Hip Score; OHS: Oxford Hip Score; UCLA: University of California at Los Angeles score; VAS: Visual Analogue Score.

surgery[352,360]. Although the QoL after two-stage revision seems comparable to aseptic revision, the QoL in the interval period (without functioning joint) is lower[9,11]. We believe one-stage revision improves quality of life for patients comparable to aseptic revision, as no interval period is needed.

Study quality

Although our study cohort is small, the study setup is retrospective, and it is a single-center observation, this is the first cohort to describe outcomes of one-stage prosthetic joint replacements in terms of quality of life. Unfortunately, no comparison with a comparable cohort after two-stage revision was possible, as only a very small group underwent resection for two-stage revision in our hospital. Also, no scores before revision surgery were available due to the retrospective nature of this study. Furthermore, the group of failures was so small (n=2), that reliable statistical analysis was not possible.

Conclusion

This study suggests excellent results of one-stage revision, with a success rate of 93%. Functional outcome and quality of life after one-stage revision are both good, and are comparable to prosthetic joint revision surgery in general. Careful and preferably predefined patient selection is required for optimal results. For further research, pre- and postoperative outcome scores are recommended. Studies comparing one-stage revision with DAIR or two-stage revision would be a welcome addition to the current studies.

CHAPTER **13**

Discussion and future perspectives

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Discussion and future perspectives

The battle against PJI seems to be quite hard to win, so far. We'll probably need a lot more research successes before we can actually beat them all of the time, instead of just winning in two thirds of the cases. Our opponent has billions of years of experience against us, but the good news: we seem to be gaining on them. We're doing much better than a couple of decades ago, which is quite fast, seeing things from the side of the microorganisms. Keep it up, people!
However, there is still much we need to research, and improve, to help us understand how PJI and biofilms work, and to help PJI patients get better outcomes and quality of life. Therefore, in this discussion, we'll talk about the different problems we still face and what could be done to improve our knowledge and outcomes after PJI, after a short review of the limitations of the studies in this thesis.

Limitations

Performing clinical studies concerning PJI can be a difficult task, because of the small number of patients developing PJI: approximately 1-2%. Even in a large regional hospital, this would lead to no more than 18 hip PJIs and 14 knee PJIs on a yearly basis. Thus, the single-center clinical studies that were included in this thesis all have small cohorts (Chapter 4, 5, 8, 12), and even the multi-center study (Chapter 9) doesn't reach 100 cases. This also causes most studies to be retrospective cohorts: prospective cohorts (Chapter 5) usually take a long time, and still often yield small cohorts. Systematic reviews (Chapter 10, 11) and meta-analyses (Chapter 3) are considered the highest level of evidence, but in PJI research they usually suffer from the quality of included studies. For that reason, only prospective studies were included in Chapter 3, but the resulting data was still heterogenous. This also applies to reviews in general, such as Chapter 7, but there is also a risk of bias in the selection process when reviews are not systematically performed. A survey study such as Chapter 2 can show interesting results, letting doctors rethink their practice. The collected data, however, is purely descriptive. Fundamental research such a laboratory studies (Chapter 6) offer results that should be reproducible and is perhaps the best way to study principles of, for example, PJI treatment. However, the downside of laboratory studies is that the experiments performed are usually not directly applicable to clinical situations, where many uncontrolled factors also play a role. Subsequent in vivo and clinical studies are always necessary. Of course, specific limitations of the Chapters are mentioned in their respective discussions.

Diagnosis: the importance of definition

Both chapters describing the results of the alpha-defensin lateral flow (AD-LF) test for PJI diagnosis of the hip (**Chapter 4 and Chapter 5**) showed good sensitivity (100%

and 83%, respectively) and specificity (89% and 92%, respectively), using the Musculoskeletal Infection Society (MSIS) criteria. These test characteristics are comparable (within the statistical margins) to the sensitivity and specificity found in **Chapter 3** for the AD -LF test (80% and 92%, respectively). When using the European Bone and Joint Infection Society (EBJIS) criteria for PJI diagnosis, the AD-LF test becomes perfectly specific, but sensitivity drops (71% in Chapter 4, 45% in Chapter 5), meaning that a lot of negative AD-LF tests are considered false-negative with this definition. When using the 2018 International Consensus Meeting (ICM 2018) criteria, the same problem arises. When excluding the inconclusive cases, the AD LF test showed high sensitivity (100% in Chapter 4, 86% in Chapter 5) and perfect specificity (100% in both Chapters). However, the 'inconclusive' cases are the most difficult ones, and should not be excluded from analysis. When including them in the PJI group (they would probably be treated as such), sensitivity decreased (91% and 53%, respectively). Unfortunately, these numbers are biased: with a positive AD test, the EBJIS criteria are fulfilled for PJI, and three (out of six) points for PJI diagnosis are received in the modified ICM 2018 criteria. The 100% specificity should be considered bearing this in mind. Also, as described in Chapter 5, there is another flaw with these PJI accuracy studies: the non-operatively treated patients, or "Schrödinger's hips", are not taken into account, which means that PJI patients may be missed. The results of all these studies could be extrapolated to other PJI patients undergoing revision surgery, but not to patients with a non-functioning arthroplasty in general.

The modified MSIS criteria have been the PJI diagnosis standard in the last decade. However, they were agreed upon by expert consensus, without real validation studies, and there were concerns about its sensitivity[19]. Therefore, the ICM 2018 definition, or rather scoring system, was meticulously developed and validated, and a very high sensitivity (97.7%) and specificity (99.5%) for PJI diagnosis were found, the sensitivity being higher than with the modified MSIS criteria (86.9%)[19]. One other validation study was published, indeed reporting a higher sensitivity for the ICM 2018 criteria (94.9%) than the modified MSIS criteria (53.1%), with a similar specificity (95.2% and 97.7%, respectively)[361]. During the actual 2018 international consensus meeting, the criteria were slightly altered[20]. One validation study was performed for these modified criteria, finding a sensitivity of 96% and specificity of 86% (for hip PJI)[362]. However, the "gold standard" to validate such criteria remains problematic, and indeed the three previously mentioned validation studies use slightly different "gold standards".

As mentioned in the Introduction, the EBJIS published a new classification in 2021, which has been included in one recent study: just like we found different test specifics with different classifications, Boechl *et al.* showed different rates of PJI when using different classification systems for PJI diagnosis in a group of patients that underwent THA revision[363].

Unfortunately, no question regarding the definition for PJI diagnosis was asked in **Chapter 2**. Of course, it wasn't such an issue back when the study was performed (the unmodified 2011 MSIS criteria had just been published, no consensus meeting had been held yet, and the EBJIS criteria didn't arrive until years later). Also, and more impor-

tantly: definition of PJI is very important for us as researchers, but it probably doesn't mean that much for the patient and the orthopedic surgeon, when they're discussing treatment options. Whether it's clearly infected or there's doubt about a single positive culture, or a cell count of 3000: the surgeon will discuss the different treatment options with the patient, and together they will choose what they think is best. That may be a staged revision because it has the highest chance of success, but it may also very well be waiting and seeing how the symptoms will develop. Deciding what's best for each individual patient is a different ball game than doing research, so, in the clinic, discussing a possible PJI with a patient, the definition is of less importance.
However, if we want to compare success rates of different treatment methods, we need uniformity. We know the success rates of two-stage revision are high, but we want to offer less debilitating options to patients, so we need to know if one-stage revision, for example, can reach the same success rates; in selected patients, or with novel techniques or agents. To truly compare our results, we should be using the same definition (and ideally, of course, this definition would be 100% sensitive, and 100% specific, and very simple, and useful in clinical practice). The ICM 2018 criteria show fairly good results, but they include a lot of tests, and what do we do with 'inconclusive' patients, both in studies and in daily practice? The latest EBJIS criteria, just like the ICM 2018 criteria, have a middle group of uncertainty ('infection likely'), which is not ideal for research purposes. The modified MSIS criteria are easier to use for studies because they're dichotomous, but are known to be less sensitive.
Both the ICM group and the EBJIS will be renewing their definitions in the years to come, in line with the newest research data. However, if they would unite and develop a single definition, that would be a huge step forward, for uniformity in research and clinical practice. Until then, it may be best to report all three definitions to optimally allow for comparison (for research purposes). Also, clinicians and researchers alike should bear in mind that there is no real gold standard, and that accuracy studies for PJI diagnosis are flawed because of "Schrödinger's hips".

Diagnosis: the importance of specific joints and microorganisms

Hip and knee PJI have been regarded as comparable: in the ICM 2018 guidelines they have been put together in the 'hip and knee' section[113], just as we have done in **Chapter 9 and 10**. Interestingly, in Chapter 3, we found lower sensitivity when using the laboratory alpha defensin test for hip PJI. As we mentioned there, that difference might have been due to bias, as only two studies were pooled for the laboratory test in subgroup analysis. On the other hand: why should test and culture results be the same for THA and TKA?
We know that different joints have different PJI properties, such as causative microorganisms, which is definitely the case for shoulder versus hip and knee PJI[101]. In a recent study, hip and knee between themselves seemed to have similar characteristics, at least for late PJI, although knee PJI showed more resistant microorganisms[364]. Other studies

have focused on *Cutibacterium* spp. as a causative microorganism in hip PJI, a bacterial species more common in the groin area[365]. *Candida* spp. are known to thrive in dark and moist areas, such as the groin, and although no clear distinction could be made in the rest of the cohort, all our own cases in Chapter 10 were hips.
So, we know there are differences in microbiome between different parts of the human skin, and the differences do not stop there: the soft tissue coverage is significantly different for hips and knee, and so are the use of bone cement, tourniquet use, materials used and the amount of material exposed. The patients are not the same, and with the rise of super-specialization, nor are the surgeons. Furthermore, diagnostic accuracy may be different too: aspiration of the knee is much easier than hip aspiration. Aspiration of hips has a higher chance of blood contamination, because it is more difficult; fluoroscopy or ultrasound needs to be used, and more often than for knees no fluid can be aspirated[366]. Blood contamination may cause more false negatives, a possible explanation for the lower sensitivity for hips found in Chapter 3. Interestingly, the only study validating the modified ICM 2018 criteria found that the criteria had slightly higher diagnostic performance for hip PJI, compared to knee PJI[362].
All of this seems a good enough reason to discriminate between joints in reports, and probably even between the approach used (for hips). When, in future research, more data can be pooled, surely the differences will become clearer.

Diagnosis: the importance of uniform guidelines

As shown in Chapter 2, standardized diagnosis and treatment was a problem in 2013. It looks like general awareness of the problem is increasing: two international consensus meetings have been held (2013 and 2018), the reports of which have been published, as well as international guidelines[8,19,20,23]. The Dutch Orthopedic Society (Nederlandse Orthopaedische Vereniging, NOV) has formed a national workgroup for orthopedic infections in 2014, which has published useful reports and guidelines. Unfortunately, we have not yet achieved international or even national unity. The European Knee Association (EKA) performed a survey in 2016, and concluded more or less the same as our study: common practice stills differs from current evidence. A survey performed in 2018 among trauma surgeons illustrated the difficulty in diagnosis and treatment of fracture related infections (FRI) by highlighting that a definition for FRI is desperately needed to develop uniform guidelines[367]. They agree that FRI and PJI are not the same, but the problems in diagnosis and treatment are, of course, comparable. A recent German survey compared PJI diagnosis and treatment regimens in between 2015 and 2020 and found a trend towards more standardized care[368], which confirms the rising awareness for the need of PJI care standardization.
Only two retrospective studies, both published in 2018, have compared adherence to guidelines with non-adherence to guidelines regarding PJI[369,370]. They found lower success rates when guidelines were not followed, but probably due to the small cohorts, the only statistically significant factors were inadequate surgical therapy (DAIR or partial

removal when full resection was advised)[369], and the absence of correct preoperative diagnostic arthrocentesis[370].
However, it also works the other way around: if some 'wrong' treatment method is commonly used, it can be established as a factor attributing to treatment failure. Several factors have thus been identified and have found their way into recent guidelines. One of the most illustrative examples may be the exchange of modular arthroplasty parts such as femoral heads and polyethylene inserts: this was (and, in many hospitals, probably still is) not always performed (in the Netherlands: 41% always, 35% sometimes, see Chapter 2), but has been described as a significant factor in achieving treatment success[41,42,371] (see **Chapter 7**), and is recommended by all recent guidelines[8,113] (although the effect seems to be less in more recent studies[372]).
Due to increasing awareness, number of PJI studies published, and several workgroups and guidelines, we are heading in the right direction: towards uniform PJI diagnosis and treatment and subsequent higher success rates. This process has already been set in motion some time ago, as can be seen in Figure 1, but there is still much room for improvement. In the Netherlands, PJI treatment has been concentrated in specialty centers in the last decade, which is a good first step. However, the first DAIR treatment, arguably the most important hit, is still usually done in the hospital where the patient had their initial arthroplasty, not always by surgeons with an arthroplasty subspecialty, and often during evening hours or weekends. Without a doubt, this leads to lower chances of treatment success for the patient. Education of surgeons and hospital staff on the importance of a thorough debridement and exchange of modular components by guidelines remains of the utmost importance. PJI networks should be established around the PJI specialty centers, for consultation with a team of orthopedic, microbiology and infectious disease specialists. Furthermore, a national PJI database is crucial if we want to compete with larger countries regarding adequately sized prospective studies.

Treatment: the importance of the biofilm

As mentioned in the introduction, PJIs are difficult to eradicate because of biofilm formation on the prosthetic components. The human immune system doesn't protect implants as it protects its own body, and so microorganisms have a chance. Most bacterial species causing PJI will form a biofilm, rendering them more resistant to the immune system and to antibiotics. This is due to the difficulty to penetrate this slimy layer, but also the lower metabolic state the bacteria transform into. Treatment becomes more difficult as the biofilm develops[26]. This battle between innate immune cells and microorganisms is called 'the race for the surface'[373]. Who ends up as the winner depends both on the number of bacteria and on the timing of inoculation[373,374].
However, biofilms do not only exist on foreign bodies. Necrotic tissue, such as bone, is another habitat for biofilm bacteria[375]. This explains why debridement is crucial, and at least partly why PJI can be so difficult to treat, even sometimes after arthroplasty removal. In other words: the biofilm is the most important factor why PJI is such a large problem.

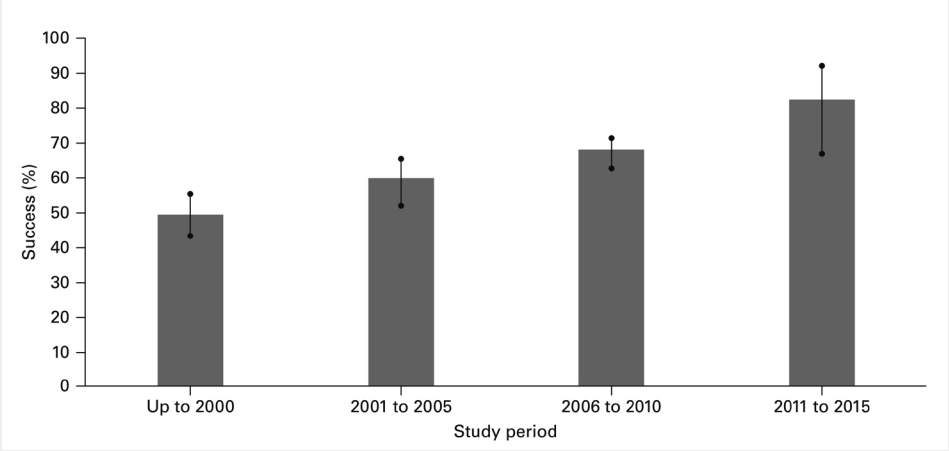

Figure 1: Pooled success rates of studies on debridement and irrigation treatment for periprosthetic joint infections of total hip arthroplasty, grouped by the end of the study period (error bars: 95% confidence intervals). Courtesy of S-T. J. Tsang, University of Edinborough, United Kingdom[371], with permission of the Bone & Joint Journal, London, United Kingdom.

To lower the impact PJI has on patients, both biofilm prevention and treatment should be improved. Prevention of biofilm formation on foreign material has been the subject of many studies in the last decades[376]. Examples of preventive measurements are antibiotic prophylaxis and skin disinfection, which are common practice, but many studies have focused on arthroplasty surface treatments such as coatings and antibiotic loaded gel[376].

In terms of biofilm eradication, current techniques consist of a combination of gross biofilm removal – with the explantation of arthroplasty components – and antibiotic treatment. When DAIR is performed and prosthetic parts are left *in situ*, biofilm removal is attempted with extensive irrigation and debridement, sometimes combined with some form of topical treatment (such as povidone-iodine). With DAIR success rates of 60-80%[371,372], there is still much room for improvement. Interestingly, a recent study found that the effect of modular component exchange on DAIR success seemed to have decreased, possibly due to other improvements[372].

Because the biofilm is the main problem is PJI treatment, novel biofilm treatment methods are crucial. In **Chapter 6**, a new substance was studied: XZ.700, specifically targeting *Staphylococcus aureus*, one of the most common and infamous PJI culprits. XZ.700 showed dislodging of the biofilm in one of the models, contrary to povidone-iodine and gentamicin. The results of this study strengthen our belief that within the next decades, biofilm removal and thus PJI treatment will be greatly improved. A combination of surgical, systemic and topical treatment specifically targeting the causative microorganism will become the standard of care.

Treatment: the importance of novel topical techniques

In the second part of this thesis, different treatment modalities are evaluated. The use of gentamicin sponges was studied in **Chapter 8** (and partly in Chapter 9), as part of local treatment protocol. Their use is safe, and high local concentrations can be achieved[130,185]. However, no significant effect on success rate has been shown, nor in Chapter 8**,** nor in other PJI studies: the use of local gentamicin sponges (and beads) was even associated with higher failure rates of DAIR for early acute PJI[377]. Even as a preventive measure, the use of gentamicin sponges did not reduce superficial or deep surgical site infection after hip hemi-arthroplasty[378]. Due to the lack of proven reduction in infection rates, their use is now discouraged in arthroplasty surgery.
Topical treatment in current practice often includes povidone-iodine (PVP-I) in 0.35% solution[114]. Recently, several studies have been published on the use of topical PVP-I (or *Betadine*), with conflicting results: some found no benefits for primary or revision arthroplasty in terms of PJI[379,380], other describe a significant reduction in PJI rates[381]. A meta-analysis published in 2021 found higher PJI reduction rates for povidone-iodine compared to saline, but the included studies were not of the highest quality[382]. For PJI treatment, povidone-iodine is one of several options for topical biofilm disruption, with some promising results in vitro, especially for immature *Staphylococcus aureus* biofilm[383]. Several other biofilm disrupting agents have been studied, including antibiotics such as bacitracin, antiseptics such as PVP-I and chlorhexidine, and antiseptic-surfactant combinations such as the commercially available Prontosan (Braun Medical) and Bactisure (Zimmer-Biomet). These agents show promising results in vitro, but cytotoxicity is a common problem, and the lack of high-quality clinical studies prevents authors from making real recommendations on the optimal topical treatment[384].
So, as far as topical treatment is concerned, no perfect solution has been found yet. The abovementioned biofilm is probably the most important factor in DAIR treatment failure. As shown in Chapter 6, it is difficult to remove the biofilm with conventional local agents such as povidone-iodine and gentamicin (in non-cytotoxic concentrations), and fully eradicate all bacteria. If we are able to remove the microorganisms' safe shelter, treatment is much more likely to be successful. In that sense, studies focusing on disruption and removal of the biofilm are key, and results such as the effect of the endolysin XZ.700 on biofilms in the dynamic model in Chapter 6 could be very important. Seeing the time-lapse movies, one hopes that endolysins such as XZ.700 will indeed turn out to be able to wipe away the biofilm. This needs to be further investigated in vivo and real-life patients, but we have hope for the future.

Outcome: the importance of the patient

In terms of outcomes, PJI studies traditionally focused on eradication of the infection, and relapse or recurrence of PJI is usually the only definition of failure. We tend to think for our patients, and what else could they want than for us to help them get rid of their complication?

In the twenty-first century, what patients themselves want has become more important, and this change will continue in the years to come. Most people will probably want to be able to walk without pain, but for some people other factors may be equally important: not undergoing surgery again, not having to stay in the hospital for weeks, being home with family and friends in the last stage of their life. It's not uncommon for people to ambulate without pain after arthroplasty resection, which could be an acceptable situation (and hence: no failure for the patient).

For the patient to be the center in this decision-making process, we need to revise our opinion of success. Patient related outcome measures (PROMs) are being used more and more in orthopedic studies. A recent study showed that patients have lower long-term PROMs scores (OHS and EQ-5D) and higher 10-year mortality after PJI compared to matched controls[385]. In **Chapter 12**, PROMs results were similar after one-stage revision for PJI compared to aseptic revisions, and successfully treated patients had a mean VAS satisfaction of 81/100. Unfortunately, no preoperative data on the same patients was available.

Describing PROMs is a good addition to studies, but those PROMs are usually secondary end points. Perhaps we should rethink the way we perform clinical studies, and make PROMs the primary aim: let the patients tell us whether they have been treated successfully or not. In that way, our way of thinking may change, and we can help PJI patients how they would like us to help them. A good example of such a patient-centered approach is a study published in 2022, that was one of the first to ask PJI patients about their decision to undergo arthroplasty surgery in the first place, and found that about a quarter of patients regretted that decision[386]. Undoubtedly, studies describing the patients' perspective will become more common in the future.

Tools helping patients in decision making have taken a flight in the last decade, and are being developed for arthroplasty surgery too, such as the SMART Choice tool for total knee replacement[387]. However, for patients suffering from PJI, there aren't many options. There is the PJI risk calculator, which could guide decision making for primary arthroplasty, giving health care professionals a PJI risk percentage, based on patient demographics and co-morbidities[388]. However, no such thing exists for people with PJI. Of course, the variety we see in patients and PJIs is significant, and often such cases are very complex. It may be an illusion that an algorithm or app could tell the patient the different options and their chances of (patient defined) success. The nuances needed to inform patients in complex cases require human interaction and years or possibly decades of experience. However, the classical paternalistic doctor, telling the patient what the next step in their treatment will have to be, is being replaced by a doctor giving the patient several treatment options, including non-surgical options.

The problems with the PJI definitions (see above) are another example of the patient not being the most important in PJI studies. As we explained in Chapter 5, "Schrödinger's hips" are patients with a painful or non-functioning total hip arthroplasty that, for various reasons, do no undergo revision surgery. Therefore, in most cases, it remains impossible to confirm or rule out PJI, and one could say they are both infected and non-infected at the same time, hence the term "Schrödinger's hips". These patients are usually exclud-

ed from studies, because they do not fit in a dichotomous PJI – not PJI. However, it would be good to know more about this group of patients, and to be able to tell them what similar patients reported, in terms of pain, function and satisfaction.

Outcome: the importance of improvements and future research

As mentioned above, PJI diagnosis, treatment and outcome have improved in the last decades, and will continue to do so. Patient reported outcome measures or PROMs are being used more and more (although still only in the minority of PJI publications), which helps us in understanding what we're doing, and will help the patient in advancing their treatment and thus outcome. For example, a recent Swedish study found higher mortality, higher need of assisted living and ambulatory aids, and lower EQ-5D and Oxford hip scores in a cohort of patients treated for PJI with minimum 10 years of follow-up, compared to matched controls[385]. Interestingly, the number of reoperations and the use of the direct lateral approach had a negative effect on the Oxford hip score.
Since registries have been set up in Scandinavia, United Kingdom, Australia, New-Zealand and the Netherlands, many studies reporting on PJI have been published, such as the abovementioned Swedish study[385]. Useful information can be gathered in such large cohorts, but registries are infamous for underreporting PJI, and up to half of PJI cases may be missed[389,390]. If the PJI diagnosis registration system can be improved in the years to come, and less PJIs are missed, registry studies could provide many new useful insights. However, at this point both the numbers of missed PJIs and the variety in outcome reporting are still somewhat problematic. For example, people suffering from PJI but refusing revision surgery will seem successfully treated in registries. The MSIS has developed a tool for classifying outcome, which could be very useful when embedded in national registries[391].
PJI collaboration projects between hospitals, within countries and even between countries in the future will give us more options for better, more accurate PJI research. Inter-hospital databases have been set up in the Netherlands, which will result in better PJI studies[390,392]. Ideally, randomized controlled trials (RCTs) should be used to further PJI knowledge. With PJI rates around 1% however, this can be difficult: even in very large hospitals, yearly PJI numbers are usually still low. To achieve numbers high enough to perform well designed RCTs, multiple hospitals should be encouraged to participate. This can be difficult, as the LEAK-study showed: a well-designed study, with many participants, trying to answer a relevant question in current orthopedic practice ("should prolonged wound leakage be treated aggressively with DAIR within two weeks?"), but patients inclusion turned out to be much slower than the expected 1.5 years, and the results have yet to be published[393]. Another promising example of an RCT in PJI research is the INFORM trial, comparing one- and two-stage revision, but in this case too, the results have not been published yet[344].

Overall conclusions

As described above, many factors are of importance in diagnosing and treating PJI. This thesis shows that in clinical practice, at least in the Netherlands and Belgium in 2013, guidelines are not uniformly followed, and improvement in that area is of the utmost importance. In recent years, new diagnostic tools, such as the alpha defensin test, have been introduced to daily practice, and patients can surely benefit from new options aiding in PJI diagnosis. The alpha defensin test shows good results for PJI diagnosis. In terms of PJI treatment, several factors have been identified that increase (or decrease) the chances of successful treatment, both in acute situations as in chronic infections, such as caused by fungi. Furthermore, the endolysin XZ.700 shows good results as a new option for topical treatment in PJI, and further studies will surely follow. Outcomes after PJI treatment, especially reported by patients, will become more important. So far, it is shown in this thesis that patient reported outcomes after both one-stage and two-stage revision for hip PJI are comparable to outcomes after hip revision surgery in general. Of course, more research is needed to provide even more substantial proof of these comparable outcomes.

Recommendations for the future

All in all, the efforts being made to advance PJI knowledge are promising. In our opinion, the future looks bright, and we will reach more significant improvements in the coming decades. However, to get to better results faster, some recommendations can be made, as described in the paragraphs above. First of all, to advance knowledge and unify research, one single definition would be ideal. Studies should be specific about the type of joint they describe, and preferably also report the approach used for hip arthroplasty. Also, uniformity in national and international guidelines, and implementation in daily practice, are essential elements to advance PJI diagnosis and treatment.
Targeting the biofilm will be the next step in PJI treatment, with topical agents to disrupt the biofilm in addition to surgical and systemic therapy. These topical agents might be antibiotics, antiseptics, endolysins or a combination.
Furthermore, the patient's preferences and demands will become more important in studies and guidelines, and our (shared) decision making should be based not only on studies reporting survival, but on a combination of factors, including what's best for each patient. For this, larger (inter-) national trials and collaborations are needed, some of which have already started.
Again: the battle isn't over, but the future does look bright indeed.

APPENDIX

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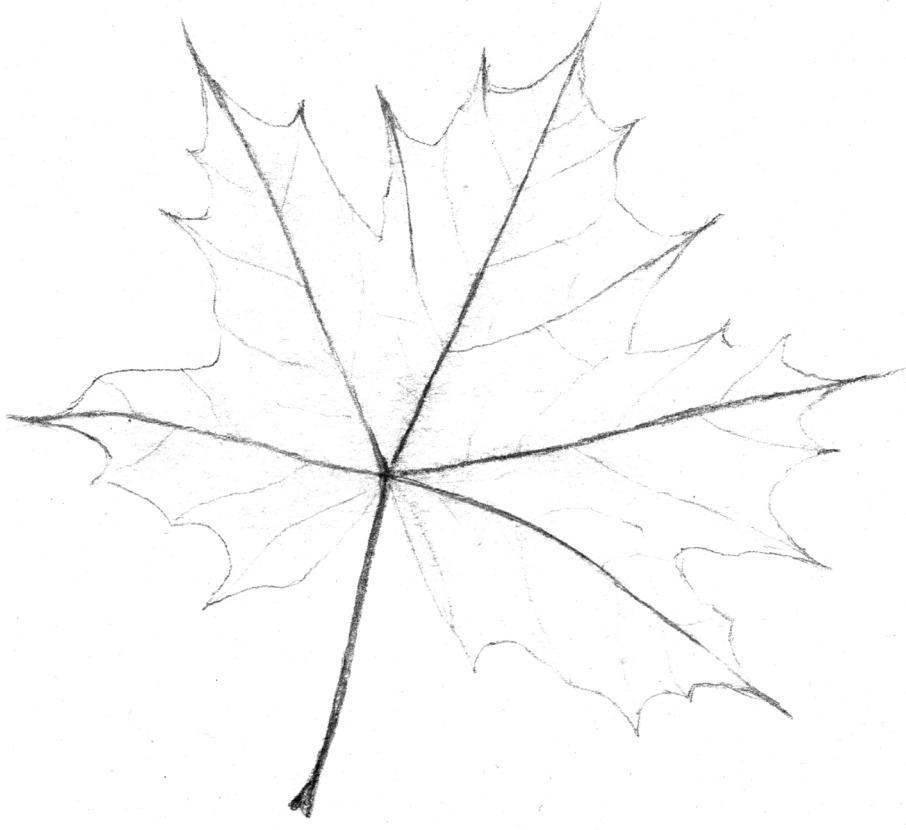
APPENDIX



GENERAL SUMMARY

Arthroplasty surgery, especially total hip arthroplasty (THA), is considered amongst the most successful surgical procedures of all time. However, complications may occur that are disabling for patients. Of all complications, periprosthetic joint infection (PJI) is one of the worst, requiring additional surgery and prolonged periods of antibiotic treatment, in a best-case scenario. In the last decades, an increasing number of studies on PJI have been performed, but we still have not won the battle against microorganisms: up to 2% of patient develop PJI after arthroplasty surgery. This thesis aims to further the cause of this fight against PJI, doing so in three main parts after the general introduction (Chapter 1): diagnosis of PJI (Chapter 2-5), treatment of PJI (Chapter 6-10), and outcomes after PJI (Chapter 11-12). In Chapter 13 (discussion and future perspectives), context is given about several important aspects around PJI, including recommendations for the future.

In the introduction (**Chapter 1**), it is described that PJI can sometimes be difficult to diagnose, and currently three different definitions are being used, each using other criteria and thresholds for PJI diagnosis. PJI is also difficult to treat, because most causative microorganisms quickly develop a biofilm, a slime layer protecting them from the patient's immune system, and from antibiotic agents. Treatment of PJI consists of both administration of antibiotic agents, and surgery; the treatment of choice depends on several different factors.

Chapter 2 represents a survey, performed in the Netherlands and Belgium. Orthopedic surgeons of approximately half the hospitals responded to the survey. Most interestingly, many differences were seen between hospitals and especially between these neighboring countries. Only a minor portion of the respondents seemed to adhere to recent guidelines, at that time.

A meta-analysis describing the sensitivity and specificity of the alpha-defensin test forms **Chapter 3**. Only prospective studies were included, both on the immunoassay-based laboratory test and the lateral flow test, including hip and knee arthroplasties. After an extensive search, four studies were included that described the laboratory test and eleven describing the lateral flow test. Both had high pooled sensitivity (90% and 86%, respectively) and very high pooled specificity (97% and 96%). A subgroup analysis was performed to compare total hip arthroplasty (THA) and total knee arthroplasty (TKA). The laboratory test was less sensitive for PJI diagnosis in hips compared to knees (70% versus 94%), but only two studies could be pooled for these data. No differences were found for the lateral flow test. The differences in sensitivity may be caused by bias, but it is recommended for all future authors to describe data on different joints separately.

Chapter 4 describes a small and retrospective study (n=52) that was performed as a pilot study on the diagnostic accuracy (sensitivity and specificity) of the alpha-defensin lateral flow test, when used for possible PJI in total hip arthroplasty. Three different PJI diagnosis criteria were described. Using the modified Musculoskeletal Infection Society (MSIS) criteria and International Consensus Meeting (ICM) 2018 criteria, the alpha-defensin lateral flow test showed high sensitivity (100% and 91%, respectively) and specificity (89% and 100%). The European Bone and Joint Infection Society (EBJIS) criteria have slightly lower thresholds, categorizing more patients as having PJ, resulting in a somewhat lower sensitivity (71%, with 97% specificity).

Encouraged by this pilot study, a prospective study on the alpha-defensin lateral flow test was started, including patients with possible PJI after total hip arthroplasty: the *SWAG* study ('*Synovasure and White blood cell count after Aspiration compared to the Gold standard*'). The results of this study are discussed in **Chapter 5**. In the final analysis, 57 patients were included. The modified MSIS criteria were used and a sensitivity of 83% and specificity of 92% were found. A second, smaller group was excluded from the analysis because they did not undergo revision surgery. However, these patients should not be dismissed: because data are incomplete, PJI cannot be confirmed or excluded. These "Schrödinger's hips", as they are called in this study, should therefore be described as a second arm in future studies.

In **Chapter 6** an in vitro study is described, in which the effect and the safety of a novel topical agent, XZ.700, are studied. XZ.700 is an endolysin, targeting the cell wall of *Staphylococcus aureus*. Two models were studied: the endolysin showed good results in the static model and performed excellently in the dynamic model, even better than two topical treatment agents that are often used in clinical practice, povidone-iodine and gentamicin. Also, XZ.700 demonstrated no toxicity on human osteocyte-like cells. **Chapter 7** is a review, describing diagnosis and treatment methods for acute PJI. Debridement, antibiotics, irrigation and implant retention (DAIR) is the treatment of choice for most acute PJIs, with success rates of 60-80%. Whether a second DAIR procedure (or even more) increases success rates remains uncertain. Factors contributing to treatment success include shorter duration of symptoms, shorter time after initial surgery and exchanging head and liner (THA) or insert (TKA).

Chapter 8 reports the results of using topical gentamicin sponges in DAIR treatment for PJI after THA. In this small retrospective cohort, the success rate was 70%. Duration of symptoms for more than four weeks was associated with treatment failure.

In **Chapter 9**, the success of DAIR treatment was studied in a larger, multicenter cohort. Including THA and TKA, 91 patients were treated with DAIR in three hospitals in the study period. Overall, a 66% success rate was found. Several factors were identified that contributed to treatment failure: a history of rheumatoid arthritis, late infection (more than two years after initial surgery), erythrocyte sedimentation rate (ESR) of more than

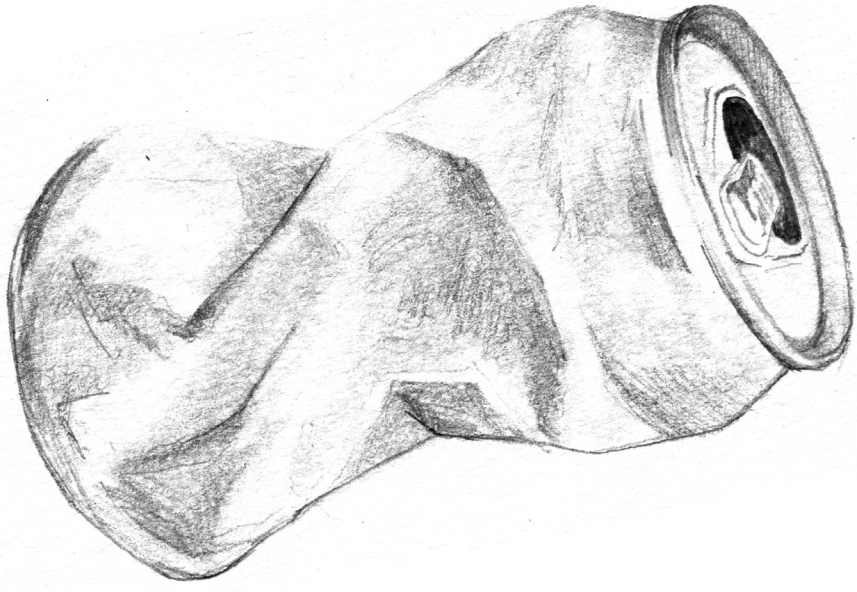
60 mm/hour at presentation, duration of symptoms of more than one week, and coagulase-negative *Staphylococcus* PJI.

Fungal PJI is very uncommon. The aim of **Chapter 10** was to shed some light on this subgroup, so a systematic review of the literature was performed, including 64 publications. After combining all described cases with eight more cases from our own institutions, the results of a total of 164 cases, treated for fungal PJI, were described. Most of the cases were caused by yeasts (*Candida* species)**.** Of 119 patients with a follow-up longer than two years, 79 were treated with two-stage revision (85% success). Two-stage revision had the highest success rate, compared to DAIR (4/22: 18%), one-stage revision (1/2: 50%), and antifungal therapy alone (0/3: 0%). In conclusion, fungal PJI should be treated, like chronic bacterial PJI, with two-stage revision.

Chapter 11 describes the results of a systematic review on two-stage revision for hip PJI on (health related) quality of life (QoL). For one-stage revision a search was also done, but no studies were found. Twelve studies reporting on outcome after two-stage revision PJI treatment were included, with overall moderate study quality. (Health related) QoL was reported using the HOOS (Hip disability and Osteoarthritis Outcome Score), WOMAC (Western Ontario and McMaster Universities Osteoarthritis Index) and SF-12 and -36 (Short Form 12 and Short Form 36). (Health related) QoL after two-stage revision was lower than in the general population, but comparable to outcomes after aseptic revision.

In **Chapter 12**, a cohort of 30 THA PJI patients is presented that was treated with one-stage revision. Functional outcomes and (health related) QoL were assessed using the HOOS, Oxford Hip Score (OHS) and EuroQoL 5 Dimensions Questionnaire (EQ-5D). Treatment success was seen in 93%. The outcome scores after one-stage revision in this cohort were high, and comparable to scores after hip revision surgery in general. **Chapter 13** concludes this thesis by discussing the different chapters, and pointing out the important items in PJI diagnosis, treatment and outcome. The different workgroups should make an effort to combine their definitions to improve both clinical practice and scientific studies. Authors should discriminate between joints and approaches used when reporting data, to create the opportunity to pool said data easily and creating homogenous pooled data sets. PJI networks and databases should be established, to improve clinical care for patients and education for doctors. More knowledge about biofilm development, prevention and eradication will become available in the coming decades, seriously furthering the cause of PJI treatment, possibly including the use of novel topical agents. More research will focus on the wishes of our patients, and treatment will probably be more tailored to specific patients in the future. With our current momentum in the battle against PJI, the future for us doctors and our patients sure looks bright.

APPENDIX



SAMENVATTING

Periprothetische infecties behoren tot de meest ingrijpende complicaties binnen de orthopedie: maandenlange behandeling met antibiotica en één of meerdere revisie-operaties betekenen dat de patiënt gebukt gaat onder grote gevolgen. Ondanks de toename in publicaties over dit onderwerp hebben we de strijd tegen de micro-organismen nog niet gewonnen: 1-2% van de patiënten met een heup- of knieprothese ontwikkelt een infectie. Dit proefschrift heeft als doel om ons verder te helpen deze infecties te bestrijden, waarbij het is onderverdeeld in introductie (Hoofdstuk 1), diagnostiek (Hoofdstuk 2-5), behandeling (Hoofdstuk 6-10) en uitkomsten na periprothetische infecties (Hoofdstuk 11-12). In Hoofdstuk 13 worden belangrijke factoren rondom periprothetische infecties behandeld, en blikken we kort vooruit naar de toekomst.

In **Hoofdstuk 1** wordt benoemd dat het lastig kan zijn om periprothetische infecties vast te stellen: er zijn momenteel drie verschillende criteria-systemen die hiervoor gehanteerd kunnen worden. Deze houden verschillende tests en andere drempelwaardes van bepaalde tests aan voor de diagnose, wat het voor de behandelaars en voor wetenschappelijk onderzoek lastig en onoverzichtelijk maakt. Verder wordt er benadrukt dat periprothetische infecties zo lastig te behandelen zijn, omdat de veroorzakende micro-organismen een 'biofilm' produceren, een slijmlaag waarin ze veel resistenter zijn voor het immuunsysteem en voor antibiotica. Daardoor is antibioticabehandeling alléén niet genoeg: er moet altijd ook een chirurgische behandeling plaatsvinden om de periprothetische infectie goed te behandelen.

Hoofdstuk 2 is een vragenlijststudie, die is uitgevoerd in Nederland en België. Van alle aangeschreven ziekenhuizen reageerde ongeveer de helft. De resultaten zijn heterogeen, maar laten duidelijk zien dat er zowel binnen de landsgrenzen als tussen Nederland en België grote verschillen zijn, en dat weinig ziekenhuizen -in elk geval ten tijde van de studie- volledig volgens de laatste richtlijnen werkten.

Hoofdstuk 3 betreft een meta-analyse waarin de sensitiviteit en specificiteit onderzocht zijn van een nieuwe diagnostische biomarker: alpha-defensine. Dit eiwit wordt geproduceerd door leukocyten in synoviaalvocht en is een aanwijzing voor periprothetische infecties. Er zijn twee tests beschikbaar: een laboratoriumtest en een sneltest (*lateral flow test*). Na een uitgebreide zoekopdracht en strenge selectie (alleen prospectieve studies werden geïncludeerd) konden vijftien studies gebruikt worden: vier over de laboratoriumtest, en elf over de sneltest. Beiden hadden goede testeigenschappen: de laboratoriumtest had een sensitiviteit van 90% en specificiteit van 97%, en de sneltest een sensitiviteit van 86% en specificiteit van 96%. Om totale heupprotheses (THP) en totale knieprotheses (TKP) met elkaar te vergelijken werd een subgroep-analyse uitgevoerd. Daarbij bleek dat de laboratoriumtest een hogere sensitiviteit had om periprothetische

infecties vast te stellen bij TKP dan bij THP (94% tegenover 70%). Dit verschil gold niet voor de specificiteit, en kon ook niet aangetoond worden voor de sneltest. Bias zou een mogelijke verklaring kunnen zijn (er konden maar twee studies gebruikt worden voor deze specifieke subgroep-analyse), maar het lijkt in elk geval aan te raden in toekomstige artikelen data betreffende de verschillende gewrichten en eventuele benaderingen apart te vermelden.

In **Hoofdstuk 4** wordt een retrospectieve, klinische studie beschreven (n=52) naar de sensitiviteit en specificiteit van de alpha-defensine-test voor periprothetische infecties van heupprotheses. Alle drie de bovengenoemde diagnostische criteria werden vermeld. Met de gemodificeerde *Musculoskeletal Infection Society* (MSIS) criteria werd een sensitiviteit van 100% en specificiteit van 89% gevonden. Wanneer de *International Consensus Meeting* (ICM) 2018 criteria gebruikt werden voor de berekening, betroffen deze waarden respectievelijk 91% en 100%. De *European Bone and Joint Infection Society* (EBJIS) criteria hebben lagere grenswaarden, wat resulteerde in een hoger aantal periprothetische infecties. De sensitiviteit met deze criteria is wat lager (71%), maar ook hier werd een hoge specificiteit gevonden (97%).

Aangemoedigd door deze resultaten, werd de prospectieve *SWAG*-studie opgezet ('*Synovasure and White blood cell count after Aspiration compared to the Gold standard*'). De resultaten van deze studie worden in **Hoofdstuk 5** besproken. In de uiteindelijke analyse werden 57 patiënten met een mogelijke periprothetische infectie van hun heupprothese geïncludeerd. Met gebruik van de gemodificeerde MSIS-criteria werd een sensitiviteit van 83% en specificiteit van 92% gevonden. Een tweede, iets kleinere groep werd niet geïncludeerd in de analyse, omdat zij geen revisieoperatie ondergaan hadden. In andere studies werd deze groep geëxcludeerd, maar dat is een vorm van bias: omdat er geen complete data van deze groep zijn, is een infectie noch uitgesloten, noch bewezen. Deze "Schrödingers heupen", zoals ze in dit hoofdstuk genoemd worden, zouden als een aparte arm beschreven moeten worden in vergelijkbare, toekomstige onderzoeken.

Hoofdstuk 6 betreft een in-vitro studie naar het effect en de veiligheid van XZ.700: een endolysine dat een specifieke werking heeft tegen *Staphylococcus aureus*. Het effect werd onderzocht met twee verschillende modellen: een statisch model waarbij biofilms op titanium gekweekt werden, en XZ.700 een goed effect had (80-90% reductie), en een dynamisch model, waarbij XZ.700 de bacteriën in de biofilm niet alleen leek te doden, maar ook de biofilm leek los te weken, waardoor deze in het model weggespoeld werd. In dat laatste model deed XZ.700 het beduidend beter dan de veel in gebruik zijnde middelen povidonjodium en gentamicine. Qua veiligheid werd aangetoond dat XZ.700 en de restproducten van de behandeling geen nadelig effect hadden op humane osteocytachtige cellen.

Hoofdstuk 7 is een review over acute periprothetische infecties. De chirurgische behandeling van eerste keus is DAIR (débridement, antibiotica en implantaat-retentie),

met een succespercentage van 60-80%. Of een tweede keer DAIR-behandeling zinvol is, wordt uit de literatuur niet helemaal duidelijk. Er zijn meerdere factoren bekend die bijdragen aan het slagen van de behandeling, waaronder kortere symptoomduur, kortere tijd na de primaire protheseplaatsing, en het wisselen van makkelijk te vervangen componenten bij een DAIR-procedure.

In **Hoofdstuk 8** wordt een studie beschreven naar het gebruik van gentamicine-matjes bij DAIR-behandeling voor infecties van totale heupprotheses. Deze matjes zijn oplosbaar en geven een hoge concentratie gentamicine, maar in dit kleine cohortonderzoek werd een succespercentage gevonden dat niet duidelijk hoger is dan vergelijkbare onderzoeken: 70%. Wel werd gevonden dat een langere duur van infectie-symptomen dan vier weken een lagere kans van slagen geeft.

Hoofdstuk 9 is een retrospectief onderzoek met een groep van 91 patiënten, uit drie ziekenhuizen, met infecties van zowel totale knie- als totale heupprotheses, die behandeld werden met DAIR; 66% werd succesvol behandeld. Verschillende factoren zorgen voor een lagere kans op succes: reumatoïde artritis, late infecties (meer dan twee jaar na de primaire prothese), een bezinking van meer dan 60 mm per uur, een symptoomduur langer dan een week, en infectie veroorzaakt door coagulase-negatieve *Staphylococcus*.

Schimmels als veroorzaker van periprothetische infecties zijn zeldzaam: ongeveer 1%. **Hoofdstuk 10** is een review die als doel had deze subgroep beter in beeld te krijgen. Een systematische beoordeling van de beschikbare literatuur leverde 64 publicaties op. Gecombineerd met acht van onze eigen casus leverde dit 164 casus op, van patiënten die behandeld werden voor een schimmelinfectie van een heup- of knieprothese. De meeste gevallen werden veroorzaakt door *Candida*. Van de 119 patiënten met een follow-up van langer dan twee jaar, waren de meesten behandeld met *two-stage*-revisie: 79 (85% succesvol). Een *one-stage*-revisie werd maar twee keer beschreven (waarvan één succesvol), en DAIR 22 keer (vier keer succesvol, 18%). Antimycotische behandeling zonder chirurgisch ingrijpen was nooit succesvol (drie casus). Geadviseerd wordt om periprothetische infecties veroorzaakt door schimmels te behandelen met *two-stage*-revisie, zoals ook bij moeilijk te behandelen bacteriële periprothetische infecties.

In **Hoofdstuk 11** worden de resultaten van een systematische review beschreven, waarin gekeken is naar uitkomsten op het gebied van kwaliteit van leven na revisiechirurgie in verband met periprothetische infecties. In de literatuur werd niks gevonden over uitkomsten na *one-stage*-revisie. Twaalf studies met uitkomsten na *two-stage*-revisie werden geïncludeerd. De gebruikte vragenlijsten om de kwaliteit van leven na deze revisies te onderzoeken waren de HOOS (*Hip disability and Osteoarthritis Outcome Score*), WOMAC (*Western Ontario and McMaster Universities Osteoarthritis Index*) en SF-12 en -36 (*Short Form* 12 en 36). De kwaliteit van leven na *two-stage*-revisie was lager dan in de algehele populatie, maar vergelijkbaar met kwaliteit van leven na heuprevisiechirurgie in het algemeen.

Hoofdstuk 12 beschrijft een studie naar de uitkomsten van *one-stage*-revisie voor periprothetische infecties van de heup. Er werd 93% succes gevonden in 30 patiënten, en de functionele uitkomsten en kwaliteit van leven -gemeten met de HOOS, *Oxford Hip Score* en *EuroQoL 5 Dimensions Questionnaire* (EQ-5D)- waren hoog, vergelijkbaar met resultaten na heuprevisies in het algemeen.

In **Hoofdstuk 13** worden de eerdere hoofstukken in dit proefschrift besproken, en worden de belangrijkste punten aangehaald wat betreft diagnose, behandeling en uitkomsten van periprothetische infecties. De verschillende werkgroepen zouden hun best moeten doen om een gecombineerde, éénduidige definitie te publiceren, om de klinische praktijk en vooral de wetenschap vooruit te helpen. Auteurs van artikelen over periprothetische infecties zouden data over verschillende gewrichten en benadering apart moeten publiceren om toekomstige meta-analyses homogener en beter te maken. Netwerken en databases voor behandeling van periprothetische infecties moeten verder ontwikkeld worden om de patiëntenzorg te verbeteren en medici beter op te leiden. Meer biofilm-onderzoek zal de komende decennia zorgen voor een duidelijker beeld en beter begrip van de biofilm, waardoor de behandeling van periprothetische infecties ook zal verbeteren. Lokale chirurgische behandeling, zoals met endolysines, kan ook een bijdrage leveren aan verbetering van de behandelresultaten. Bovendien zal toekomstig onderzoek zich steeds meer richten op de wensen van de patiënt, zoals de onderzoeken naar kwaliteit van leven. Ook de behandeling van patiënten met periprothetische infecties zal steeds vaker *à la carte* zijn. Met de verbeteringen in diagnostiek, behandeling en uitkomsten van periprothetische infecties, die we hopelijk in de komende tijd kunnen verwachten, ziet de toekomst er rooskleurig uit.

APPENDIX

ABBREVIATIONS

α-MEM	Minimum Essential Medium Alpha modification	Cell culture medium, used in cell biology experiments
AAA	Amsterdam Active Attachment biofilm model	A biofilm model developed to study active biofilm attachment by suspending materials in medium, thus removing the effect of gravity
AD	Alpha-Defensin	Biomarker, produced by neutrophils in synovial fluid; higher levels indicate local infection
AD LF	Alpha-Defensin Lateral Flow test	Point-of-care test for alpha-defensin in synovial fluid, designed to confirm periprosthetic joint infection
ALTR	Adverse Local Tissue Reaction	A combination of immune-mediated tissue reactions related to local metal or polyethylene debris
ANOVA	ANalysis Of VAriance	Statistical test to analyze variance between groups
ASA	American Society of Anesthesiologists	The ASA has developed the ASA score to classify patients' fitness for surgery or anesthesia
BMI	Body Mass Index	A measurement of body size, calculated by dividing weight in kilograms by height in meters squared
BSA	Bovine Serum Albumin	Albumin derived from cows, sometimes used in experiments

CFU	Colony Forming Units	A microbiology unit, estimating the number of viable microorganisms in a sample
CI	Confidence Interval	The range of values that you expect your estimate to fall between a certain percentage of the time (usually 95%) if you run your experiment again or re-sample the population in the same way
CNS	Coagulase-Negative *Staphylococcus*	Coagulase-negative *Staphylococci* are gram-positive, aerobic bacteria, distinguished from the closely related *Staphylococcus aureus* by the group's inability to form coagulase
CoC	Ceramic on Ceramic (hip articulation)	Prosthetic hip articulation with a ceramic head (ball) and a ceramic liner (socket)
CoP	Ceramic on Polyethylene (hip articulation)	Prosthetic hip articulation with a ceramic head (ball) and a polyethylene liner (socket)
COPD	Chronic Obstructive Pulmonary Disease	A group of diseases causing airflow blockage and breathing-related problems, including emphysema and chronic bronchitis
CRP	C-Reactive Protein	A protein produced by the liver in response to inflammation
DAIR	Debridement, Antibiotics, Irrigation and implant Retention	Surgical treatment for (acute) periprosthetic joint infection, in which the prosthesis is retained

DM	Diabetes Mellitus	A metabolic disease that causes high blood sugar
DNA	DeoxyriboNucleic Acid	Molecule that carries genetic information
DR	Dedicated Room	
DTT	DiThioThreitol	A small-molecule redox reagent with the ability to dislodge biofilm bacteria
EBJIS	European Bone and Joint Infection Society	European association of orthopedic surgeons, microbiologists and infectious disease specialists
EKA	European Knee Association	European association of orthopedic (knee) surgeons
ELISA	Enzyme-Linked ImmunoSorbent Assay	Laboratory method to detect a substance using an antibody and enzyme
EQ-5D	EuroQoL 5 Dimensions Questionnaire	Questionnaire designed to assess quality of life
ESR	Erythrocyte Sedimentation Rate	The rate of sedimentation of red blood cells in millimeters per hour, a marker of inflammation
EUCAST	EUropean Committee on Antimicrobial Susceptibility Testing	European network of established experts in the determination of antimicrobial breakpoints and in antimicrobial susceptibility testing
FC1	FetalClone1	Brand of artificial serum used in laboratory experiments
FITC	Fluorescein IsoThioCyanate	Fluorescent molecule used in experiments

FN	False Negative	Negative test result in a patient that does have the disease the test is supposed to detect
FP	False Positive	Positive test result in a patient that does not have the disease the test is supposed to detect
FRI	Fracture Related Infections	Infections occurring after surgery performed for traumatic bone injuries
FU	Follow-Up	Time between treatment and last contact or reexamination of a patient
GFP	Green Fluorescent Protein	Protein that exhibits bright green fluorescence when exposed to ultraviolet light
GFR	Glomerular Filtration Rate	Filtration rate of the kidneys, an index of kidney function
GM	GentaMicin	Antibiotic agent of the aminoglycoside group. Heat resistant, and therefore often used in bone cement
HHA	Hip Hemi-Arthroplasty	Replacement of the head of the hip, usually performed after a fracture of the femoral neck. The pelvic part of the hip (acetabulum) is left intact, as opposed to a total hip arthroplasty
HHS	Harris Hip Score	An outcome score designed to evaluate hip function after hip surgery

HPF	High Power Field	The field of view under the maximum magnification power of the microscope used (usually 400x)
HOOS	Hip disability and Osteoarthritis Outcome Score	An outcome score designed to evaluate hip function after hip surgery
(HR)QoL	(Health Related) Quality of Life	The domains of quality of life (the patients' own appreciation of physical, mental and social well-being), influenced by health status and problems
ICM	International Consensus Meeting	International meeting of orthopedic surgeons, infectious disease specialists and medical microbiologists, trying to reach consensus in controversial matters regarding PJI, held in 2013 and 2018
ICPC	International Classification of Primary Care	Classification method for primary care encounters, which can be used to search a database for patients with specific diseases
IDSA	Infectious Diseases Society of America	American society of infectious disease specialists
IQR	InterQuartile Range	The spread difference between the 75th and 25th percentiles of the data, or middle 50%.
LE	Leukocyte Esterase	An esterase produced by leukocytes; can be used to test for the presence of white blood cells

LF	Lateral Flow	Type of test device used to confirm the presence or absence of a target substance; pregnancy tests are the best-known example
LS	Laboratory Staff	People working in a laboratory
MAP	Merle d'Aubigné-Postel functional score	An outcome score designed to evaluate hip function after hip surgery
MB	MicroBiologist	
MCS	Mental Component Score (part of SF-12 and SF-36)	
MINORS	Methodological Index for NOn-Randomized Studies	An instrument designed to assess the methodological quality of non-randomized surgical studies
MoM	Metal on Metal (hip articulation)	Prosthetic hip articulation with a metal head (ball) and a metal liner (socket)
MoP	Metal on Polyethylene (hip articulation)	Prosthetic hip articulation with a metal head (ball) and a polyethylene liner (socket)
MRSA	Methicillin Resistant *Staphylococcus Aureus*	Strains of *S. aureus* that display drug resistance to beta-lactam antibiotics, such as penicillin (and methicillin)
MSIS	Musculoskeletal Infection Society	American society for the advancement of knowledge in the field of musculoskeletal infection

MSSA	Methicillin Sensitive *Staphylococcus Aureus*	Strains of *S. aureus* that show no resistance to beta-lactam antibiotics, such as penicillin (and methicillin)
NOV	Nederlandse Orthopaedische Vereniging (*Dutch Orthopedic Society)*	Dutch society of orthopedic surgeons
NPV	Negative Predictive Value	The proportion of negative results in statistics and diagnostic tests that is true negative
OHS	Oxford Hip Score	An outcome score designed to evaluate hip function after hip surgery
OP	OutPatient clinic	
OR	Operating Room	
OS	Orthopedic Surgeon	
PA	PAthologist/PAthology	
PBS	Phosphate Buffered Saline	Buffer solution commonly used in biological research
PCR	Polymerase Chain Reaction	Laboratory method to rapidly make large amounts of copies of a specific DNA sample, allowing scientists to take a very small sample of DNA and amplify it to a large enough amount to study in detail
PCS	Physical Component Score (part of SF-12 and SF-36)	

PI	Propidium Iodine	A popular red-fluorescent nuclear and chromosome counterstain, commonly used to detect dead cells in a population
PJI	Periprosthetic Joint Infection	
PMMA	PolyMethylMethAcrylate	Chemical compound, also known as bone cement
PMN	PolyMorphonuclear Neutrophils (neutrophil granulocytes)	Type of white blood cell, important part of the immune system, and an indicator of inflammation
PO	PeriOperative	
PPV	Positive Predictive Value	The proportion of positive results in statistics and diagnostic tests that is true positive
PRISMA	Preferred Reporting Items for Systematic reviews and Meta-Analyses	System with a set of items for reporting used for research (systematic reviews and meta-analyses)
PROMs	Patient Reported Outcome Measures	Health outcome directly reported by the patient who experienced it
PSF	Penicillin, Streptomycin, and Fungizone-mix	Mix of antibiotics used in cell biology to prevent contamination of cell cultures
PVP-I	Povidone-Iodine (PolyVinylPyrrolidon-Iodine)	A disinfectant complex, consisting of the water soluble PVP and iodine

QALY	Quality-Adjusted Life-Years	Generic measure of disease burden, including both the quality and the quantity of life lived (one QALY equates to one year in perfect health)
QUADAS-2	Quality Assessment of Diagnostic Accuracy Studies-2	System for assessment of the quality of primary diagnostic accuracy studies
QoL	Quality of Life	An individual's perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards and concerns
RCT	Randomized Clinical Trial	A form of scientific experiment used to control factors not under direct experimental control, by comparing a new treatment to a standard of care or placebo.
RD	Radiology Department	
SD	Standard Deviation	A measure of the amount of variation of a set of values
SF-12	Short Form 12	Questionnaire for patients designed to assess mental and physical health status, in 12 questions (developed because for some respondents 36 questions was too great a burden)
SF-36	Short Form 36	Questionnaire for patients designed to assess mental and physical health status, in 36 questions

SWAG	Synovasure and White blood cell count after Aspiration compared to the Gold standard	Prospective study designed to evaluate the Synovasure (alpha-defensin) lateral flow test
TFA	Total Femur Arthroplasty	Surgical replacement of the upper leg (femur), including hip and knee, usually reserved for complex cases (e.g., cancer)
THA	Total Hip Arthroplasty	Surgical replacement of the hip joint, both the ball (femoral head) and the socket (acetabulum)
TKA	Total Knee Arthroplasty	Surgical replacement of the knee joint, both the upper leg (femur) and lower leg (tibia)
TN	True Negative	Negative test result in a patient that does not have the disease the test is supposed to detect
TP	True Positive	Positive test result in a patient that does have the disease the test is supposed to detect
TSA	Total Shoulder Arthroplasty / Tryptic Soy Agar	Surgical replacement of the shoulder joint, including ball (humeral head) and socket (glenoid) / Medium used to culture bacteria on a culture plate
TSB	Tryptic Soy Broth	Liquid medium used to culture bacteria
UCLA	University of California at Los Angeles activity score	A ten-point rating scale rating activity, ranging from 1 (inactivity, cannot leave residence) to 10 (regularly participates in impact sports)

VAS	Visual Analogue Score	Continuous rating scale for pain (of another outcome), on which a patient can draw a line anywhere between 0 and 100 on a line (usually 100 mm).
VM	VancoMycin	Antibiotic agent (for intravenous use) that (in orthopedics) is usually reserved for difficult to treat infections such as caused by methicillin resistant *Staphylococcus aureus* and methicillin resistant *Staphylococcus epidermidis*
WBC	White Blood Cell count	Measure of number of white blood cells (leukocytes) in blood or any other fluid, indicating inflammation
WOMAC	Western Ontario and McMaster Universities Osteoarthritis Index	Outcome score developed to assess the course of disease or response to treatment in patients with knee or hip osteoarthritis

APPENDIX

AUTHOR CONTRIBUTIONS

Chapter 2 Variety in diagnosis and treatment of periprosthetic joint infections in Belgium and the Netherlands

Kuiper JWP (JK), Vos CJ (CV), Burger BJ (BB), Colen S (SC)
Acta Orthopaedica Belgica 2016
JK, BB, and SC conceived and designed the study. JK performed the literature search and contacted the hospitals. JK and SC analyzed the data and wrote the manuscript. All authors contributed to interpretation of the data and revision of the final manuscript.

Chapter 3 Does the Alpha Defensin ELISA test perform better than the Alpha Defensin lateral flow test for PJI diagnosis? A systematic review and meta-analysis of prospective studies

Kuiper JWP (JK), Verberne SJ (SV), Vos CJ (CV), van Egmond PW (PE)
Clinical Orthopaedics and Related Research 2020
JK conceived and designed the study and performed the literature search. JK, SV and PE analyzed the data and wrote the manuscript. All authors contributed to interpretation of the data and revision of the final manuscript.

Chapter 4 Good accuracy of the alpha-defensin lateral flow test for hip PJI: a pilot study in a retrospective cohort of 52 patients

Kuiper JWP (JK), Pander P (PP), Vos CJ (CV)
World Journal of Orthopedics 2020
JK and CV conceived and designed the study. JK and PP performed the literature search, collected the data, analyzed the data and wrote the manuscript. All authors contributed to interpretation of the data and revision of the final manuscript.

Chapter 5 Are accuracy studies for PJI diagnosis inherently flawed? And what to do with Schrödinger's hips? A prospective analysis of the alpha defensin lateral flow test in chronic painful hip arthroplasties

Kuiper JWP (JK), Verberne SJ (SV), van Egmond PW (PE), Slot K (KS), Temmerman OPP (OT), Vos CJ (CV)
Hip & Pelvis 2022
JK and CV conceived and designed the study. JK and SV performed the literature search. JK, SV and KS collected the data. JK, SV and PE

analyzed the data and wrote the manuscript. All authors contributed to interpretation of the data and revision of the final manuscript.

Treatment of periprosthetic joint infections

Chapter 6 The novel endolysin XZ.700 effectively treats MRSA biofilms in two biofilm models without showing toxicity on human bone cells in vitro

Kuiper JWP (JK), Hogervorst JMA (JH), Herpers BL (BH), Bakker AD (AB), Klein Nulend J (JKN), Nolte PA (PN), Krom BP (BK)
Biofouling 2021
JK, BH, JKN, PN and BK conceived and designed the study. JK, AB and BK performed the literature search. JK, JH and BK collected the data. JK and BK analyzed the data and wrote the manuscript. All authors contributed to interpretation of the data and revision of the final manuscript.

Chapter 7 Treatment of acute periprosthetic infections with prosthesis retention: review of current concepts

Kuiper JWP (JK), Tjeenk Willink R (RTW), Moojen DJ (DM), van den Bekerom MPJ (MB), Colen S (SC)
World Journal of Orthopedics 2014
JK, MB, and SC conceived and designed the study. JK, DM and SC performed the literature search. JK, RTW, DM, and SC analyzed the data and wrote the manuscript. All authors contributed to interpretation of the data and revision of the final manuscript.

Chapter 8 Implantation of resorbable gentamicin loaded sponges in addition to irrigation and debridement in 34 patients with infection complicating total hip arthroplasty

Kuiper JWP (JK), Brohet RM (RB), Wassink S (SW), van den Bekerom MPJ (MB), Nolte PA (PN), Vergroesen DA (DV)
Hip International 2013
JK, PN, and DV conceived and designed the study. JK, SW, PN and DV provided study material or patients. JK and RB analyzed the data. JK wrote the manuscript. All authors contributed to interpretation of the data and revision of the final manuscript.

Chapter 9 Prosthetic joint associated infections treated with DAIR (debridement, antibiotics, irrigation, retention) in the Netherlands: analysis of risk factors and local antibiotic carriers

Kuiper JWP (JK), Vos CJ (CV), Saouti R (RS), Vergroesen DA (DV), Graat HCA (HG), Debets-Ossenkopp YJ (YDO), Peters EJG (EP), Nolte PA (PN)
Acta Orthopaedica 2013
JK, SV, RS, HG, DV, and PN contributed to the conception and design of the study and to provision of the study patients. JK, SV, and RS collected data. JK wrote the protocol, analyzed data, and wrote the manuscript. All the authors contributed to interpretation of the data and to revision of the final manuscript.

Chapter 10 Two-stage revision recommended for treatment of fungal hip and knee periprosthetic joint infections

Kuiper JWP (JK), van den Bekerom MPJ (MB), van der Stappen J (JS), Nolte PA (PN), Colen S (SC)
Acta Orthopaedica 2013
JK, MB, and SC conceived and designed the study. JK and SC performed the literature search. JK, SC, and JS analyzed the data and wrote the manuscript. All authors contributed to interpretation of the data and revision of the final manuscript.

Outcomes after periprosthetic joint infections

Chapter 8 Quality of life after staged revision for infected total hip arthroplasty

Kuiper JWP (JK), Rietbergen L (LR), Walgrave S (SW), Hak L (LH)†, Colen S (SC)
Hip International 2016
JK and SC conceived and designed the study. JK, LR, SW and SC performed the literature search. JK, LR and SC analyzed the data and wrote the manuscript. All authors contributed to interpretation of the data and revision of the final manuscript.

Chapter 12 Results and patient reported outcome measures (PROMs) after one-stage revision for periprosthetic joint infection of the hip: a single-center retrospective study

Kuiper JWP (JK), Rustenburg CME (CR), Willems JH (JW), Verberne SJ (SV), Peters EJG (EP), Saouti R (RS)
Journal of Bone and Joint Infection 2018
JK and CR conceived and designed the study. JK, CR and SV performed the literature search. CR contacted the patients. JK, CR, JW and SV analyzed the data and wrote the manuscript. All authors contributed to interpretation of the data and revision of the final manuscript.

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PUBLICATIONS

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Kuiper JWP, Hogervorst JMA, Herpers BL, Bakker AD, Klein Nulend J, Krom BP, Nolte PA. The novel endolysin XZ.700 effectively treats MRSA biofilms in two biofilm models without showing toxicity on human bone cells in vitro. *Biofouling. 2021; 37(2):184-193.*

Kuiper JWP, Verberne SJ, van Egmond PW, Slot K, Temmerman OPP, Vos CJ. Are accuracy studies for PJI diagnosis inherently flawed? And what to do with Schrödinger's hips? A prospective analysis of the alpha defensin lateral flow test in chronic painful hip arthroplasties. *Hip & Pelvis. 2022; 34(4):236-244.*

APPENDIX

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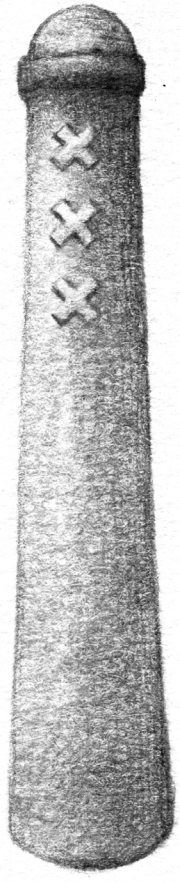
APPENDIX



ABOUT THE AUTHOR

Jesse Kuiper was born in Amsterdam on the 25th of October 1984, where he grew up with his brother Mikko and sister Ellemijn. After graduating the Ignatius Gymnasium in 2002, he started his Medicine studies at the VU University in 2003. He did his first research project, on hamstrings flexibility and subsequent injuries, at Amsterdam football club Ajax. During his internships he started with his first orthopedic research, on periprosthetic joint infections. After graduating in 2010, he started working in orthopedic surgery in Zaandam and Alkmaar, and worked at the Centre for Orthopaedic Research Alkmaar (CORAL) for a year. In 2012 he spent three months in the ACTA Amsterdam laboratory for research. He started his orthopedic training in 2013, doing rotations at the Spaarne Gasthuis, Noordwest Ziekenhuisgroep and VUmc, during which he published several of his studies.

In 2017, he married the love of his life Renée, and their son Oscar was born. In 2019, he spent another three months in the ACTA laboratory to perform his in-vitro-study. After finishing his training in 2020, Jesse, Renée and Oscar left the Netherlands to visit New-Zealand for three months, which was cut short by COVID-19 after four weeks. They spent seven weeks on Rarotonga, a small tropical island in the Pacific, before being able to continue their journey to Toronto, Canada. There they lived for a year while Jesse did his fellowship *lower extremity reconstruction* at the Michael Garron Hospital. In 2021, their second son Pieter was born in Toronto, and when travelling became possible in the summer of 2021, the four of them decided to travel across Canada for two months after finishing the fellowship.

In September 2021, they returned to the Netherlands, and Jesse started working at the Ommelander Ziekenhuis Groningen in Scheemda. After three months, he started a new position as a arthroplasty revision fellow at the Catharina Ziekenhuis in Eindhoven. In October 2022, the family moved to Drenthe when Jesse started as staff orthopedic surgeon at the Martini Ziekenhuis in Groningen. A month later their daughter Anna was born, and they will be moving to their newly built home in Peize in 2024. In his free time he likes to play board games with his friends, bake artisanal pizza, play video games, eat at fancy restaurants with Renée, play football, have dinner with friends, and read.