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## Prosthetic joint infections: new diagnostic and therapeutic strategies

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## CHAPTER 8

# **Summary and general discussion**



The road to improved outcome for patients with a prosthetic joint infection is challenging and requires multidisciplinary collaboration. The evidence for diagnostic and treatment strategies for PJI is scarce as demonstrated by the international consensus meeting in 2018 in the United States during which expert-based consensus about diagnosis and treatment was reached by voting. In The Netherlands, this lack of evidence is reflected by much practice variation between different PJI treatment centers, even at geographically adjacent hospitals. In 2015, orthopedic surgeons, infectious diseases specialists and medical microbiologists from several regional hospitals increasingly felt the need to develop scientific evidence by comparing the then used protocols for treatment of PJI. Further, we aimed to cooperate and harmonize the practice variation in our region. A diagnostic and treatment protocol was developed by all participating centers, weekly multidisciplinary meetings were organized and data were collected prospectively in a regional quality registry. This collaboration increased not only job satisfaction but resulted in a more scientific approach leading to important insights as summarized in this thesis. Next to the scientific evaluation of clinical treatment strategies, translational research is needed to understand the exact pathophysiologic mechanism of surviving persisters in a biofilm. Such knowledge charts the scientific route to innovative anti-persister treatment strategies. In this chapter, three key outcomes of the research, described in this thesis, will be summarized and discussed.

### **The use of E health to detect prosthetic joint infections**

The *first* part focuses on the role of mobile E-health aimed at earlier detection of PJI. In **chapter 2**, the introduction of a postoperative woundcare app, which was developed to increase patient involvement and to shorten the time to PJI diagnosis, is described. In this study, we focused on assessing the ease of use and perceived usefulness of this app in a group of sixty-nine patients in two hospitals. The use of this app was evaluated by patients with a high perceived usefulness and ease of use. The patient-reported and physician-reported outcome were identical in 80% of cases. The high self-reported perceived usefulness and ease of use was the reason to set up a larger, multicenter study in which the same app was used to gain better insight in the duration and amount of wound leakage in patient who developed a PJI and in patients with an uncomplicated course. In **chapter 3**, the results of this study were summarized. From this study, it appeared that PJI was very unlikely in postoperative patients without any wound leakage or other signs of wound infection. Postoperative wound leakage in the first week after arthroplasty frequently occurred (50%) and was not related to PJI. Apparently, this early wound leakage can be regarded as a natural postoperative course which is only relevant if the wound continues to leak over the next weeks. Wound leakage in the second or third week however was strongly associated with the occurrence of PJI, but its positive predictive value was low. For example, any amount of wound leakage in the third

postoperative week was strongly associated with PJI (OR 51, 95% CI 11-227, sensitivity 88%, specificity 88%). However, the positive predicted value was only 11%, which would result in an unacceptable number of 10 patients needed to DAIR to diagnose and treat one real PJI. We estimate that host characteristics such as weight, presence of diabetes mellitus, and use of anticoagulants may lead to a longer duration of wound leakage rather than being a sign of early wound infection. In contrast, moderate to heavy leakage in the third postoperative week predicted PJI with much higher specificity (PPV 83%) resulting in a Number Needed to DAIR to diagnose one patient with PJI of 1.2 patients.

How should the result of this study influence daily practice? One consequence may be that outpatient wound care follow-up after arthroplasty may be reduced or even cancelled for patients who report no leakage and no other complications during the postoperative period. Outpatient follow up may still be needed for evaluation of mobility, strength and other functional tests which cannot be performed with telemonitoring. An important learning point is that early wound leakage after arthroplasty belongs to the natural postoperative course, except if it lasts longer than two weeks or increases in quantity. Even in the third postoperative week, mild leakage is still found in many patients with an uncomplicated course.

The wound care app was intended to improve patient engagement and prevent delay in the diagnosis of PJI. Many patients (42%) felt more involved due to using the app while less patients (15%) felt partly involved or not / only a bit involved (28%). We suspect that patients with an excellent outcome without complications are less in need of an app to feel more involved in care. Another question is whether the use of the app attributed to earlier diagnosis of complications. The median time-to-DAIR in our study was 16 days. Only 2 PJIs (13%) were diagnosed between week 4 and 12 after arthroplasty. These differential time-to-DAIR is short if compared to data from a recent Dutch study in which the differential time-to-DAIR for most patients was between four and twelve weeks after arthroplasty (56% of knee PJIs and 36% of hip PJIs). In a Swedish cohort, the differential time-to-DAIR was 20 days for patients with total hip arthroplasty.<sup>1</sup> Three of the six patients with an eventual PJI in our study were earlier admitted or seen at the outpatient clinic after an alert-based phone call to the hospital. This shows the app's potential to speed up the diagnosis of prosthetic infection. However, the small number of patients with PJI in our study necessitates cautious conclusions. A randomized controlled trial in which the time to DAIR for PJI is compared in patients with and without the use of a wound care app, would answer this question. The app used in this study specifically targeted wound leakage and signs of wound infection. Ideally, such an application should not be a standalone wound leakage app but a more general perioperative app in which all aspects of perioperative care for patients are integrated. Based on the current study, the algorithm should be adjusted to reduce unnecessary alerts to patients. The predictive value of the algorithm may be improved by using a machine

learning algorithm, where changes can be made to the algorithm automatically, based on mounting collected data. Adding laboratory parameters like an increase in C-reactive protein may also increase the yield of the algorithm. Based on the current study, less value should be placed on minimal wound leakage and low pain scores, as these were not discriminatory for the development of PJI.

### **Evaluation of current antimicrobial strategies for PJI**

The *second* part of this thesis focuses on the evaluation of different antimicrobial treatment strategies for PJI. In **chapter 4** all studies reporting the outcome of staphylococcal PJI after DAIR over the last 30 years were assessed in a systematic review and meta-analysis, focused on the use of rifampicin for staphylococcal PJI. One of the conclusions of this study was the persistently low success rates after DAIR, although there was a trend toward increasing success rates over the years. The added value of rifampicin, compared with other treatment strategies for staphylococcal prosthetic joint infections, appeared to be marginal. The trim-and-fill analysis done in our systematic review suggested publication bias. Correction for this bias resulted in an adjusted relative risk of success of 1.04 (95%CI 0.94 to 1.14) when rifampicin was used.

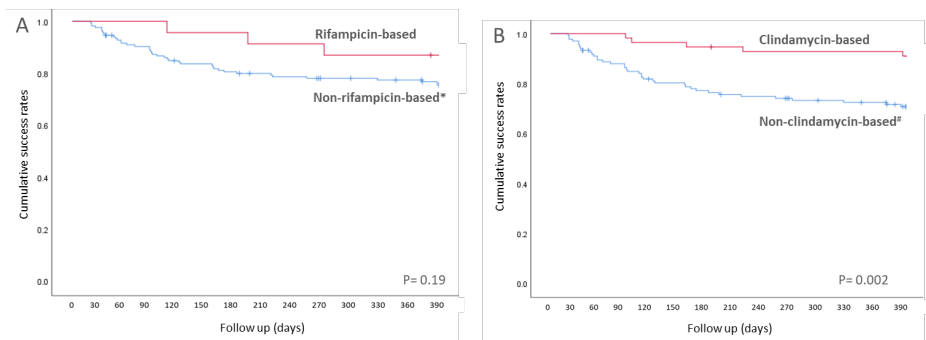
Despite the limited evidence for the effectiveness of rifampicin, the recommendations to use rifampicin in staphylococcal prosthetic joint infections are strong in most guidelines. Several explanations for this can be given. The study by Zimmerli et al., in which almost all patients recovered after treatment with DAIR and combination treatment with rifampicin, was published in 1998. At that time the outcome after DAIR for PJI was regarded as poor, although large cohort studies before 1998 do not exist. Although the trial was heavily underpowered, including only 18 patients with a PJI, the good outcome in the group treated with rifampicin was in line with several experimental foreign body animal models showing high cure rates if rifampicin combination treatment was used. Meanwhile, the use of rifampicin is widely implemented in the care of patients with infected implants. Our systematic review, described in **chapter 4**, was the first review that systematically appraised all studies regarding the outcome of staphylococcal PJI. The methodological quality of most observational studies in which the use of rifampicin for PJI was evaluated, was poor. To initiate scientific discussion on methodological limitations in observational studies on rifampicin, we wrote two letters to the editor. In these letters, we drew attention to the various forms of bias and confounding in observational studies on PJI. In **chapter 4** we contested the conclusions of an observational study in which authors concluded that prolonged duration of rifampicin therapy was a key determinant for improved outcomes in acute staphylococcal PJI treated with DAIR. However, this outcome may be explained by (1) exclusion of patients who failed during treatment with rifampicin (exclusion bias) , (2) confounding by indication by not prescribing rifampicin

to patients with a higher apriori risk of therapy failure and (3) immortal time bias by prescribing rifampicin only to patients who did not have treatment failure in the first postoperative weeks after the DAIR. In **chapter 4**, we also discussed the study by Beldman et al, who demonstrated a statistically significant association between rifampicin use and treatment success in pooled cohorts<sup>2</sup> However, confounding and immortal time bias were still likely to be present and cannot be fully adjusted for in a multivariate analysis. An important limitation of observational PJI studies is the comparison between rifampicin and non-rifampicin treatment strategies. Comparison of one well-defined strategy (rifampicin combination therapy) with all other non-defined strategies (including all varieties of antimicrobial options without rifampicin) will, together with the forms of bias described above, likely result in an underestimation of the effectiveness of all regimens included in the non-rifampicin strategies. This bias in favor of a well-defined treatment strategy may lead to unjustified rejection of equally good alternatives within the non-defined treatment group. This is further elaborated under the next heading.

The risk of PJI in patients undergoing endoprosthetic reconstruction of the lower extremities after tumor surgery is high and often requires multiple surgical interventions. In **chapter 5** we focused on outcome after surgical debridement for patients with an infected megaprosthesis after tumour surgery. We found more polymicrobial infections in these patients compared to PJI after conventional arthroplasty. This is in line with an earlier study by our group in which 25% of patients had polymicrobial PJI.<sup>3</sup> The success rate of DAIR for an infected megaprosthesis was 50%. The chance of eradicating the infection after each subsequent DAIR was approximately 30-50%. This low success rate may be related to the chronicity of infections (35% had a DAIR for chronic PJI more than 12 weeks after index surgery), a known risk factor for failure after DAIR. Complete exchange of the megaprosthesis when infected may enhance cure rates but a much more complicated surgical procedure is needed for this strategy. Practically, it also takes more time to construct a new custom-made tumour prosthesis, making a one-stage exchange of acutely infected tumour prostheses more challenging. Weighing all these arguments, performing one or more DAIR procedures appears to be a viable treatment option for patients for whom there is no contraindication to DAIR.

### **New antimicrobial strategies for PJI: antibiotic treatment**

To better understand the group of patients not treated with rifampicin, we analyzed data from patients with staphylococcal PJI treated with alternative strategies. In **chapter 6**, we analyzed data from 200 patients with staphylococcal PJI in our prospective observational clinical registry. In this group of patients, clindamycin-based treatment was found to be more effective than non-clindamycin-based treatment, but for the same group of patients, rifampicin-based treatment was also more effective than non-rifampicin-based treatment (Figure 1).



**Figure 1.** Outcome after DAIR related to antimicrobial strategy

This analysis clearly demonstrates the limitation of comparing treatment strategies if one of the group is poorly defined. To overcome this issue, we classified patients in several well-defined antimicrobial treatment groups. This enabled us to draw relevant conclusions about the effectivity of different regimens. A treatment strategy with either clindamycin or flucloxacillin and only five days of rifampicin was found to be as effective as traditional long-term rifampicin combination therapy. This non-inferiority was achieved even at a four-week shorter treatment duration in the patients treated with flucloxacillin or clindamycin. The results of this study are in line with the results of an earlier report, also described in **Chapter 6**. Here, the use of targeted oral flucloxacillin monotherapy for staphylococcal PJI is reported in a small observational cohort study. A success rate of 83% is reported in patients with staphylococcal hip PJI and 44% in staphylococcal knee PJI treated with flucloxacillin monotherapy and only five days of rifampicin, started immediately postoperative. Both studies are the first reports indicating that reasonable cure rates can be achieved with alternative targeted strategies with antimicrobial monotherapy. However, confounding is also present in this study and groups. The groups were well defined but not always comparable. Clindamycin, for example, was only prescribed at the time of the iv-oral switch. Patients in this group probably had a more favorable prognosis than those for whom it was deemed necessary to continue treatment with intravenous flucloxacillin and who were therefore assigned to the flucloxacillin group. This can only be solved with randomisation. Therefore, based on the findings described in this thesis, a randomized controlled trial is needed to directly compare clindamycin or flucloxacillin monotherapy with rifampicin combination therapy.

In the past 30 years, two randomized studies have been conducted to answer this question. The first study, published in 1998, showed a significantly better outcome when rifampicin was used but failure in the control group was mainly caused by ciprofloxacin resistance and the study included only 18 patients with prosthetic joint infection<sup>4</sup>. A larger, more



recent study including 48 patients was published in 2020 and showed no difference between treatment with or without rifampicin<sup>5</sup>. Both studies were underpowered due to low inclusion rates. Therefore, the most recent study did not lead to a change in guidelines. The lack of good evidence, the disadvantages of long-term combination therapy with rifampicin and fluoroquinolones, the toxicities and drug-drug interactions associated with the use of rifampicin and the need for equivalent treatment alternatives justify the set up of a new trial. Therefore, in 2023, a multicenter study will start in the Netherlands in which patients will be randomized between clindamycin monotherapy and rifampicin/levofloxacin combination therapy during the oral treatment phase of prosthetic joint infections caused by staphylococci (**Rifampicin Combination Therapy versus Targeted Antimicrobial Monotherapy** in the oral antimicrobial treatment phase of staphylococcal prosthetic joint infection; the RiCOTTA trial).

There are few clinical data about the optimal timing of starting rifampicin in the treatment of PJI. Treatment with rifampicin may result in selection of rifampicin-resistant coagulase-negative staphylococci on the skin that could potentially infect the prosthesis via the postoperative wound and cause a secondary superinfection of the prosthesis. However, clinical data supporting this risk are lacking, and withholding an adequate bactericidal agent because of a possible complication seems illogical. In the two cohort studies in this thesis (**chapter 6**), in which rifampicin was started immediately postoperative, only one patient developed a relapse with a rifampicin-resistant *S. aureus*, one year after the DAIR. Because of the time elapsed since surgery, this resistance was probably not related to the five days of rifampicin treatment one year before. In the randomized controlled trial by Zimmerli et al., rifampicin was also started immediately postoperatively and did not result in rifampicin-resistant staphylococci in patients with a relapse.<sup>4</sup> In addition, in vitro studies show that rifampicin resistance only develops under the condition of a high bacterial load and if rifampicin is given as monotherapy. During DAIR, the bacterial load is significantly reduced intraoperatively and rifampicin is always started as combination therapy. Based on all these data, we therefore consider immediate postoperative initiation of rifampicin safe

### **New antimicrobial strategies for PJI: anti-persister treatment**

Innovative strategies to eradicate biofilm-embedded bacteria are the focus of the *third* part of this thesis. Persister cells residing within chronic biofilms are the root cause of relapse of biofilm-associated infections because they cannot be targeted by antibiotics. In **chapter 7**, we confirmed the antibiotic recalcitrance of biofilms by demonstrating that highly bactericidal antibiotics (rifampicin combined with ciprofloxacin) were not able to eradicate persisters within a mature biofilm. Therefore, the development of alternative anti-persister drugs is necessary to cure biofilm-associated infections. If such a drug

would be available, surgery for PJI and many other biofilm-associated infections like vascular graft infections, prosthetic valve endocarditis, fracture-related infections, spinal implant infections and infected cardiac devices may be no longer needed. Unfortunately, the global preclinical antibacterial pipeline does not include any anti-persister drug. However, several anti-persister treatment strategies have been developed or the last decades which may lead to clinical application in the future. Antimicrobial peptides have broad antibacterial activities and have shown activity against persisters.<sup>6</sup> SAAP-148 is an antimicrobial peptide, developed at LUMC, which is effective under physiological conditions (i.e., in 50% human plasma) and has broad antimicrobial activity against MRSA and Gram-negative bacteria in ex vivo and in vivo wound infections.<sup>6</sup> We decided to optimize preclinical research models with chronic biofilms on abiotic surfaces to test anti-persister drugs. In **chapter 7**, we report on the development of an in vitro mature biofilm model. With this model we aimed to develop an innovative way to simulate a PJI as much as possible, creating optimal conditions to create a mature biofilm as is the case in patients with a PJI. With this approach we tried to avoid outcomes of in vitro experiments that may not be optimal for translation to clinical biofilm-associated infections. We assessed the effectivity of anti-biofilm and anti-persister agents on polystyrene plates, titanium/aluminium/niobium discs and prosthetic joint liners. Bacteria obtained from and residing within these biofilms were eradicated after exposure to SAAP-148, acyldepsipeptide-4, LL-37 and pexiganan. SAAP-148 also eradicated bacteria within the antibiotic-exposed, mature biofilms on all surfaces, indicating that SAAP-148 is highly effective against persisters within these models. This mature biofilms on different abiotic surfaces can be further used to test other novel treatment strategies like bacteriophages, quorum sensing inhibitors and other antimicrobial peptides. Application of SAAP-148 in an ointment solution on an infected implant as additional treatment during surgical debridement would be a relevant clinical application which needs further investigation.

## Concluding remarks

Accurate self-monitoring of postoperative wounds after joint implantation helped elucidate the course of wound leakage and its association with acute prosthetic joint infections. The collection of clinical data on different antimicrobial treatment strategies provided insight into the effectiveness of different treatment options for patients with a prosthetic joint infection. In this thesis, we report that personalized antimicrobial treatment for prosthetic joint infections is possible without compromising the effectiveness of treatment. In the coming years, the role of different oral treatment strategies will be further studied in the already mentioned multicenter RiCOTTA study in the Netherlands. In addition, this thesis describes the role and importance of new anti-persister drugs against biofilm-associated infections. We developed a biofilm model that closely resembles the clinic of a prosthetic joint infection. This allowed us to investigate the effectiveness of innovative anti-biofilm drugs. Based on the results described in this thesis, future research will be aimed at better understanding the pathogenesis of biofilms. The effectiveness of new drugs against biofilms can be investigated in this biofilm model. This should ultimately lead to better treatment options for patients with a prosthetic joint infection, ultimately achieving the goal: better care for vulnerable patients who are confronted with a serious postoperative complication.

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