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Prosthetic joint infections: new diagnostic and therapeutic strategies

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CHAPTER 1

Introduction and outline of the thesis

Introduction[1]

A prosthetic joint infection (PJI) is a serious complication of arthroplasty often leading to long-term hospitalization, severely restricted mobility and reduced quality of life.[4] The surgical treatment options for PJI are dependent on the chronicity of the infection and host characteristics. In most cases of acute PJI, surgical debridement with retention of the prosthesis, followed by antimicrobial treatment, is the preferred treatment strategy (summarized as 'DAIR': Debridement, Antibiotics and Implant Retention). For chronic PJI, the implant often needs to be removed. Surgical treatment is followed by long-term antimicrobial treatment. Despite well-defined surgical and antimicrobial treatment strategies, failure rates are still considerably high. Reported failure rates vary between 10 and 70% due to heterogeneity in patient populations, type of PJI and different surgical and antimicrobial treatment strategies.[5,6] An important reason for treatment failure is the existence of a biofilm on the surface of the implant. This biofilm consists of a matrix of proteins and nucleic acids in which bacteria can escape the activity of the immune system and can switch to metabolically inactive bacteria, called persisters, against which antibiotics are ineffective.[7] Both the composition and the characteristics of a biofilm explain why curing biofilm-associated infections in general, such as prosthetic joint infections, central line-associated bloodstream infections, infected cardiac devices and vascular graft infections is notoriously difficult. Often, these infections can only be cured if the foreign device is removed, but this is accompanied by major inconvenience for the patient due to prolonged immobility and the need for reoperation to insert a new prosthesis. However, cure may also be achieved after surgical debridement and keeping the prosthesis in situ. It is generally believed that the chance for eradication of infection increases if the time interval between inoculation of bacteria on the implant and surgical debridement is short, although some studies show contradictory results.[8-10] Consequently, a delay in making the diagnosis may cause more chronic infections and lower success rates after DAIR. Removal and delayed reimplantation of the infected joint is an alternative surgical approach for PJI but this is associated with long-term immobility, longer hospital admissions and surgical-related secondary infections. To improve outcome for patients with PJI, both early detection and adequate treatment strategies are important factors for successful treatment. In this introduction, the clinical presentation of acute and chronic PJI and the composition of biofilms are described. Next, a historical overview of the

1 This introduction is based on three earlier publications in NTvG, NVMM and a conference paper from the Boerhaave Posteducational Course on Infectious Diseases in 2018.1. Scheper H, Wouthuyzen-Bakker M, Veldkamp KE, et al. [Prosthetic joint infection]. *Ned Tijdschr Geneeskd* 2019;163, 2. Scheper H RM, M.G.J. de Boer. Geinfecteerde gewrichtsprotheses. Nascholingscursus Infectieziekten 2018. Noordwijkerhout, 2018:27-44, 3. H. Scheper S.A.V van Asten, R.J.P van der Wal, M.G.J. de Boer. Rifampicin for orthopedic infections: a hstorical overview. *Ned Tijdsch Med Microbiol* 2020;28(3):110-17.

antimicrobial treatment strategies for PJI including the use of rifampicin for staphylococcal PJI will be provided. Finally, we formulate the questions underlying this thesis.

In the current literature, PJI is mostly spelled out as prosthetic joint infection but also as periprosthetic joint infection or sometimes prosthetic joint-associated infection. The difference between these terms is merely semantic. A PJI also implicates that bone and surrounding tissues are involved in the infection. In line with the nomenclature that is already in vogue for other biofilm-associated infections, for this thesis the term prosthetic joint infection is consistently used (like in prosthetic valve endocarditis and vascular graft infection).

Epidemiology of PJI

Annually, over 70.000 hip and knee prostheses are implanted in patients in the Netherlands.[11] These operations are generally successful and cost-effective.[12] Due to the aging of the population, the number of implanted joint prostheses, and thus the number of PJI will continue to increase. For the United States of America, it is estimated that more than 3.400.000 prosthetic joints will be implanted in 2030 with a yearly count of 26.000 hip PJIs and 40.000 knee PJIs.[13]

The incidence of PJI after primary arthroplasty is estimated to be 1,5-2% per year.[13,14] After joint revision surgery (approximately 5000 revision procedures per year in the Netherlands), the proportion of PJI is much higher. In the Dutch Arthroplasty Register (LROI), nearly all implanted prosthetic joints are registered. However, in this registry, revision surgery is only recorded if a part of the prosthetic joint is removed or exchanged. Also, patients with PJI who are not operated but only treated with antibiotics are not recorded in this register. Therefore, the actual incidence of PJI is likely to be higher, around 3-5% as recently illustrated in papers from different countries.[15,16]

Pathogenesis and microbiology

Curation of PJI is notoriously difficult due to the formation of a biofilm on the surface of the implant. Known microorganisms associated with biofilm formation are *Staphylococcus aureus*, coagulase-negative staphylococcus (CNS), *Candida albicans*, *Pseudomonas aeruginosa* and *Cutibacterium acnes*, but almost every bacterium can form a biofilm[17]. A biofilm gives a bacterium survival advantage and develops as soon as bacteria adhere to foreign material. The degree of adhesion is determined by, among other things, the nature and roughness of the surface, electromechanical forces, flow velocity around the material, pH, presence of antibiotics, granulocytes, and properties of the bacterium itself (hydrophobicity cell surface, fimbriae, flagellae)[18]. A matrix of extracellular polymeric substances (EPS)

containing proteins, polysaccharides and nucleic acids is formed in which bacteria can proliferate, communicate and escape the activity of antibiotics and the hosts immune system[19]. Most likely, the ineffectiveness of antibiotics to eradicate bacteria from biofilms is not explained by reduced penetration in the biofilm or by antimicrobial resistance. Antibiotics generally penetrate well into biofilms, although sometimes with a delay[20-22]. The main problem of biofilm-associated infections is the presence of persisters[7]. A small proportion of bacteria in the biofilm will, secondary to stress, absence of nutrients or by stochastic variation, switch phenotypically from planktonic bacteria to dormant 'persisters'. Persisters are metabolically inactive bacteria that survive high local antibiotics concentrations because antibiotics can only target dividing bacteria[23]. The knowledge of the existence of persisters dates back to shortly after the introduction of penicillin[24]. In vitro, penicillin was found not to be able to completely kill a population of *S. aureus*. When the small subpopulation of surviving bacteria was incubated again after discontinuing penicillin, it was found to be equally sensitive for penicillin after re-exposure to penicillin. This could be repeated several time without resistance occurring. The surviving bacteria after antibiotic exposure were named persisters.

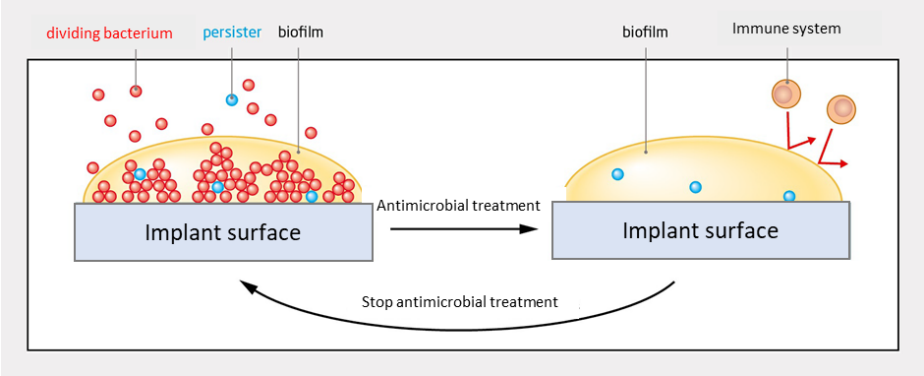

Figure 1. Effect of antimicrobial treatment on bacteria within a biofilm on an implant

In the following decades, limited research has been performed on persisters. During this period, bacteria were referred to as planktonic, free-living, dividing single cells. Since the late seventies, the research landscape changed. The term biofilm was coined in 1981 by Costerton et al. who described the presence of surface-adhering bacteria embedded in a 'glycocalyx' matrix.[25] In the decades thereafter, the molecular mechanisms enabling bacteria to switch to and from a metabolically inactive state were increasingly unraveled.[26-30] The biofilm protects bacteria against eradication by antibiotics and /or the hosts immune defense. Some antibiotics such as rifampicin and fluoroquinolones are able to effectively penetrate a biofilm and therefore often called 'biofilm-active' agents. However, given the dormant state of persisters, it is unlikely that these antibiotics

can eradicate persisters residing in biofilms.[16]. Additionally, it is unknown how long persisters within chronic biofilms are able to survive under chronic antibiotic pressure.

Clinical presentation
The clinical presentation of an acute PJI differs from a chronic PJI. This is because low-virulent pathogens, such as *Staphylococcus epidermidis* and *Cutibacterium acnes*, particularly involved in chronic PJI, lead to a different clinical presentation than, for example, *S. aureus* and streptococci, which due to their virulence give a more acute clinical presentation. Acute PJI during the first weeks after joint arthroplasty can be characterized by acute wound deterioration, swelling of the wound, wound leakage, fever or elevated inflammatory parameters (Table 1)[1]. Acute PJI may also occur years later if a virulent micro-organisms adhere to the prosthesis via haematogenic route or per continuitatem via a nearby focus.

Chronic PJI is characterized by a more prolonged postoperative course of swelling, persistent wound leakage and fistula formation. This may be accompanied by subfebrile body temperature and mildly increased CRP or BSE but inflammatory parameters can also be completely within the normal range. Sometimes, the only clinical sign for a chronic PJI is a loosened prosthesis, or chronic discomfort and/or pain. Differentiation between acute and chronic PJI is relevant because the different causative micro-organisms in acute and chronic PJI require a different antibiotic and surgical strategy. Further, chances for cure appear to decline once an infection becomes more chronic. For practical reasons and to be able to compare studies a schedule of the different clinical presentation was constructed that may be helpful when discussing patients or when comparing patient populations in different studies (Table 1).

Postoperative wound leakage as diagnostic factor for PJI

Persistent postoperative wound leakage is regarded as an important risk factor for PJI.[33-36] However, wound leakage may also be secondary to physiological processes such as fatty necrosis or temporary serosanguinous leakage caused by intraoperative disruption of capillaries.[36] Insight in postoperative wound leakage data is crucial for clinicians who must weigh whether persistent wound leakage in postoperative patients are signs of a PJI, requiring reoperation, or belong to an uncomplicated course, not requiring reoperation. It has been hypothesized that an early DAIR for patients with prolonged wound leakage after arthroplasty may reduce later revision surgery. This is in line with a strong recommendation from an international PJI consensus meeting.[37]

However, quantitative data about postoperative wound leakage after arthroplasty in patients with and without PJI are lacking.[38] This lack of evidence results in a large variety of expert- (but not evidence-) based diagnostic and treatment strategies in daily practice.

Tabel 1. Characteristics of acute and chronic prosthetic joint infection

Characteristic	acute PJI (symptoms ≤ 3 weeks)		chronic PJI (symptoms > 3 weeks)	
	early	**late**	**early**	**late**
Estimated prevalence[31 32]	25%	30%	20%	25%
Time arthroplasty to infection	≤ 3 weeks	months-years	3 weeks - 3 months	> 3 months
Route of infection	exogeneous*	hematogeneous spread or nearby focus	exogeneous*	exogeneous*
Clinical presentation	wound dehiscence, warmth, wound leakage, fever, increase in CRP	acute pain, swelling with or without fever	swelling, warmth, persistent wound leakage, sinus tract, subfebrile temperature, mildly elevated CRP	chronic pain, loosening of prosthesis, sinus tract
Most common causative micro-organisms	*Staphylococcus aureus*, *Enterobacterales*	streptococci, *S. aureus*, *Enterobacterales*	Coagulase-negative staphylococci, enterococci	Coagulase-negative staphylococci, *Corynebacterium Cutibacterium acnes*
Surgical treatment	DAIR	DAIR	DAIR or replacement of prosthesis	replacement of prosthesis

DAIR = 'debridement, antibiotics and implant retention'.

* Infectie due to per- or postoperative colonization of wound.

The likelihood of having a PJI increases if a postoperative patient not only has wound leakage but also other classic signs of infection like fever and redness. Differentiation between a 'superficial' wound infection without involvement of the implant and PJI is extremely difficult. Animal experiments show that in a postoperative wound after arthroplasty only 50-100 bacteria are needed to cause a PJI compared to 10.000-100.000 bacteria needed to cause a wound infection in a postoperative wound without an implant.[39] Therefore, given the high bacterial load in a clinically visible wound infection, it is generally believed that a PJI should be excluded in all patients who present with a wound infection after arthroplasty.. Empirical treatment with antibiotics prior to adequate diagnostics is strongly discouraged, because this delays the diagnostic process, it may lead to false-negative cultures and it will not cure an established PJI after all.

Causative micro-organisms of PJI

The micro-organisms most frequently isolated in patients with PJI are dependent on the type of joint, time elapsed since the implantation and the type of surgery (primary

arthroplasty or tumour reconstruction surgery). For acute knee or hip PJI during the early postoperative period after arthroplasty (usually within the first one month) *Staphylococcus aureus* (30-50%), Coagulase negative staphylococcus (13-30%), *Enterobacteriaceae* (4-16%) and streptococci are the most frequently isolated pathogens 8-16%). Chronic PJI is mainly caused by Coagulase-negative staphylococcus (27-35%), *Cutibacterium acnes* (formerly known as *Propionibacterium acnes*; 6-12%) and polymicrobial flora (911%).[31 32 40] Acute hematogenic infections are predominantly caused by streptococci and *S. aureus* and nearly always monomicrobial.[32 41] In 10-35% of patients, cultures remain negative, although very low culture-negative PJI (1%) was reported in one study.[31 32]. The risk of a negative cultures can be reduced by a standardized method of processing intraoperative cultures and by an antibiotic-free interval before cultures are collected (ideally two weeks prior to diagnosis if possible).

Diagnostic Criteria of PJI

A PJI is suspected based on the clinical presentation, often increased inflammatory parameters and can be confirmed with positive cultures of synovial fluid or intraoperative biopsies or positive histopathological examination. There is not a serological marker with a 100% sensitivity or specificity for PJI. In recent years, a number of organizations have established diagnostic criteria for an prosthetic joint infection (Table 2). The presence of pus, fistula or an identical micro-organism in at least 2 deep-tissue cultures is considered to be definitive evidence for a PJI. Supporting criteria include increased inflammatory parameters, only one positive culture in several deep tissue samples, an increased leukocyte number or an increased percentage of neutrophile granulocytes in the synovial fluid. The release of bacteria from biofilms by sonification appears to be a useful additional tool to increase the sensitivity of cultures, especially in patients with chronic infection with low-virulent microorganisms or in patients pretreated with antibiotics.[42] More research is needed to assess how novel diagnostic biomarkers in synovial fluid and blood can be used as a diagnostic criterium.[43] The European diagnostic criteria were recently updated by the European Bone and Joint Infection Society (Table 2).[44]

Surgical treatment

The most important goal of surgical debridement is the removal of all infected tissue including the biofilm on the prosthesis. In patients with acute PJI, cure of infection with retention of the implant is pursued. In order to achieve this, extensive surgical debridement is needed, also called DAIR (Debridement, Antibiotics and Implant Retention, see Figure 2). The surgically accessible parts of the implant are thoroughly cleaned and the replaceable prosthesis parts ('polyethylene liner', femoral head, insert ('insert') of the acetabulum) are replaced. For patients with chronic PJI or patients with a loose prosthesis infection, chances to cure PJI are much lower when treated with DAIR as described above.[45] In general,

these patients needs removal of the prosthesis during surgical debridement, followed by antibiotic treatment and delayed reimplantation during a second operation. This is called a two-stage exchange procedure. The reimplantation of a new prosthetic joint can also be performed immediately during the same surgical procedure in which the infected joint is removed, called a one-stage exchange. Observational studies show a reinfection rated between 0% and 41% in two-stage exchange studies and between 0% and 11% in one-stage exchange studies, but no randomized controlled trials have been published yet.[46]

Antimicrobial treatment

The antibiotic therapy is directed against the infection in the tissue around the prosthesis and against surviving bacteria on the implant after surgical debridement. During the postoperative period after debridement, new biofilm formation after debridement needs to be prevented at all costs. Therefore, effective treatment should be started a soon as possible after the operation. The choice of antimicrobial strategy depends on the susceptibility of the causative pathogen, the comedication that is used, documented allergies or intolerances and hosts factors like medical history and patient adherence. Patients are treated with long-term antimicrobial treatment, usually between six and twelve weeks.[47] In the recently published DATIPO trial 6 weeks of antibiotic therapy were inferior to 12 weeks of antibiotic therapy in patients with PJI treated with DAIR or one-stage exchange.[48] This study contradicted the results of a number of observational studies in which a shorter treatment period (6-8 weeks) was also sufficient.[49-51] Failure of treatment may be secondary to residual (infected) cement, a secondary infection with another micro-organism after surgical debridement, improper antibiotic use, reduced compliance to therapy, or antibiotic resistance of the causative micro-organism. Often, in these patients the prosthetic joint needs to be removed.

The use of rifampicin-based antibiotic strategies for staphylococcal PJI

Many studies have reported outcome of PJI after surgical debridement in order to evaluate an antibiotic treatment strategy for staphylococcal PJI. Most of these studies were observational retrospective studies. For staphylococcal PJI, two randomized controlled trials were published about the adjunctive value of rifampicin combination therapy for staphylococcal PJI. Over the last decennia, rifampicin has become the cornerstone of treatment for acute staphylococcal PJI.[52 53] Unfortunately, the use of rifampicin is hampered by drug-drug interactions and significant side effects.[54] Therefore, safe and effective alternative antimicrobial regimens for PJI are needed, but comparative data evaluating a rifampicin-based strategy with other antimicrobial strategies, such as clindamycin, levofloxacin or flucloxacillin, are nearly absent. This paragraph gives a historical overview of the (history of the) role of rifampicin combination therapy for orthopedic infections.

Table 2. Diagnostic criteria for PJI according to American and European scientific societies

	MSIS 2011	IDSA 2013	ICM 2018	EBJIS 2021
Confirmative criteria*				
pus around the prosthetic joint		•		
sinus tract	•	•	•	•
same microorganism in ≥ 2 intraoperative samples	•	•	•	•
virulent microorganism in ≥ 1 intraoperative sample		•		
leukocyte count >3000/µl or >80% PMN in synovial fluid				•
Positive α-defensin in synovial fluid				•
acute inflammation in histopathologic examination‡				•
>50CFU/ml any organism on sonication				•
Supportive criteria‖				
Preoperative:				
Clinical features: early radiographic loosening, CRP>10, wound healing problem, purulence around prosthesis, recent fever or bacteremia				•
elevated CRP- of D-dimer concentration	•		• (2 p)	
ESR > 30 mm/h			• (1 p)	
Positive α-defensin in synovial fluid			• (3 p)	
CRP > 6,9 mg/l in synovial fluid			• (1 p)	
leukocyte count > 3000/µl in synovial fluid	•		• (3 p)	
leukocyte count > 1500/µl or >65% PMN in synovial fluid				•
> 80% granulocytes in synovial fluid			• (2 p)	•
Intraoperative:				
pus around the prosthetic joint	•		• (3 p)	•
virulent microorganism in ≥ 1 intraoperative sample	•	•	• (2 p)	•
acute inflammation in histopathologic sample ‡	•	•	• (3 p)	
>1 CFU/ml any organism on sonication				•

IDSA = Infectious Diseases Society of America; MSIS = Musculoskeletal Infection Society; ICM = International Consensus Meeting on Musculoskeletal Infection (Philadelphia, 2018); EBJIS = European Bone and Joint Infection Society. ESR = erythrocyte sedimentation rate, CRP = C-reactive protein. PMN = polymorphonuclear neutrophils. P = points.

* PJI is confirmed, according to this societies in the presence of >1 confirmative criteria

‡ Presence of ≥ 5 neutrophils in ≥ 5 high-powerfields (400 x) *or* visible micro-organisms

‖ According to MSIS, PJI is confirmed in the presence of at least 4 supporting criteria. According to ICM, *preoperatively*, PJI is confirmed if at least 6 p, PJI is likely if 2 to 5 p; no PJI if 0 to 1 point. *Intraaoperatively*, PJI is confirmed if at least 6 p; PJI may be present if 4 to 5 p, no PJI if 0 to 3 p. According to EBJIS, PJI confirmed if at least 1 confirmative criterium, PJI likely if combination of 2 supporting criteria, requiring 1 clinical feature and 1 laboratory feature

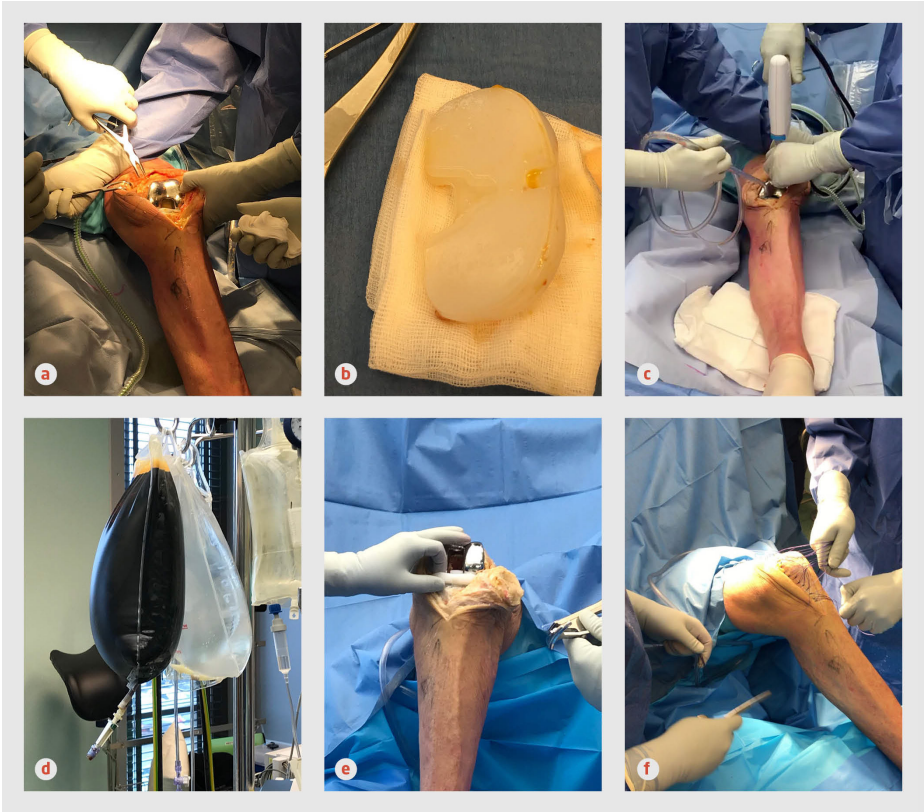

Figure 2. Surgical debridement of an infected knee implant

Legend. (a) During debridement, the joint is opened, multiple deep-tissue cultures are taken and infected tissue is removed. (b) The exchangeable prosthetic parts, such as this liner of the knee prosthesis, are replaced. After removing the liner, the surgeon also has better access to the surgical area that needs to be de debrided. (c) and (d). The joint is rinsed extensively with sodium chloride mixed with an antiseptic such as iodine with the 'pulsed lavage' technique. (e) Then, the surgical area is re-covered with clean drapings and a new liner is inserted. (f) Afterwards the wound is closed. (Scheper et al. Ned Tijdschrift v Geneeskunde 2019, *pictures obtained from Drs. R Mahdad, Alrijne hospital*)

The discovery of rifampicin

Rifampicin owes its name to Piero Sensi, an Italian scientist who had the habit of giving nicknames to newly discovered antibiotics. In 1957, his Milanese research group isolated, from a French soil sample, a new class of antibiotics from the bacterium *Amycolatopsis rifamycinica* (previously called *Streptomyces mediterranei* and subsequently called *Nocardia mediterranea*).[55] This new antibiotic class, called rifamycins, were named after the then famous French gangster film Rififi (French for "trouble"), directed by Jules Dassin. The abbreviation of the active ingredient (N-**A**mino-N-**M**ethyl**P**iperazine) completed the name. The first rifamycin for clinical use, rifamycin SV, was replaced by rifampicin due

to better bioavailability and effectiveness, especially against *Mycobacterium tuberculosis*. Later it was also found to be very effective against *Mycobacterium leprae*.[56] Rifampicin kills bacteria by binding to the β-subunit of the DNA-dependent RNA polymerase, resulting in blocking of the transcription process and consequent inhibition of bacterial RNA synthesis.[57] Rifampicin diffuses freely into tissues and bacteria and is highly effective against Gram-positive and some Gram-negative bacteria and also has bactericidal activity on intracellular microorganisms. The drug came on the market in 1968, and is now, more than 50 years later, still an essential part of tuberculostatic treatment. Resistance against rifampicin quickly occurs by a single mutation in the rpoB gene, which encodes the β-subunit of the RNA polymerase.[57] This resistance may occur within 48 hours when rifampicin is used as monotherapy or in the treatment of infections with a very high bacterial load[58]. The fear for widespread rifampicin resistance in such a powerful anti-tuberculous drug resulted in a strong lobby, led by pulmonologists, to discourage the use of rifampicin for non-tuberculous infections. However, that fear turned out to be unjustified in 1980 when a study showed that the incidence of rifampicin-resistant tuberculosis strains in countries where rifampicin was freely used in combination therapy for urinary and respiratory infections was not higher than in countries with highly restrictive use of rifampicin only for tuberculosis.[59]

Experimental animal studies about PJI

In 1973, Mandell et al. reported that of 18 antibiotics tested, only rifampicin was able to kill intracellularly dividing bacteria in macrophages that had survived phagocytosis.[60] Interestingly, rifampicin did not kill inactive intracellular bacteria that had been metabolized by cooling to non-dividing state. This led the authors to suspect that there was no specific mechanism of action for rifampicin, but mainly a good intracellular penetration. Later, several studies confirmed the excellent penetration of rifampicin into biofilms, but persisters could not be killed with rifampicin.[61 62] In 1983, the group of Waldvogel showed in the first animal study that rifampicin monotherapy, when administered three hours before to twelve hours after inoculation of *S. aureus* in a Teflon cage which was placed in the flank of guinea pigs, prevented infection[63]. If rifampicin was administered after twelve hours of inoculation, infection developed with growth of rifampicin-resistant *S. aureus*. Since then, at least seven experimental animal studies in guinea pigs with implanted Teflon cages have been performed by groups directed by Zimmerli et al.[64] In these studies, the time from inoculation to initiation of antibiotics was between 24 and 72 hours. The duration of treatment with rifampicin lasted four days. Betalactam antibiotics and clindamycin could not be tested because these antibiotics induced severe weight loss in the guinea pigs within four days. The cure rate with rifampicin/fluoroquinolone combination therapy in the guinea pigs in these studies was 88-100%. Monotherapy with fluoroquinolones, vancomycin, daptomycin or

linezolid resulted in a cure of 0% in six out of seven studies. In another experimental animal model, rats with artificial implants were treated, after 14 days of inoculation with MRSA, with six days of rifampicin combination therapy. None of the animals were cured.[65]

In all the described animal experiments above, debridement of the infected implant was not part of treatment. Apparently, the duration of biofilm formation and possibly also the innate immune system of the type of animal have a crucial influence on the effectiveness of the antibiotic treatment.

Rifampicin for PJI: outcome in randomized controlled trials

In 1974 Bourret et al. in the *Lyon Medical* were the first to report a 'very satisfactory clinical effect' with rifampicin combination therapy for osteomyelitis caused by staphylococci (original article not traceable anymore). In 1979 some clinical studies were summarized in which the usefulness of rifampicin was also described in other non-tuberculous microorganisms. Rifampicin combination therapy seemed particularly promising for staphylococcal infections.[66] In a small randomized prospective study in the 1980s, patients with chronic *S. aureus* osteomyelitis (i.e. without artificial material) were randomized between nafcillin monotherapy (cure 4 out of 8 patients) and nafcillin-rifampicin combination therapy (cure 8 out of 10 patients).[67] Next, a randomized controlled trial (RCT) in 101 patients with *S. aureus* infection showed no benefit with rifampicin combination therapy; in a subgroup of 23 osteomyelitis patients, rifampicin/oxacillin (or rifampicin/vancomycin) combination therapy appeared to be more effective.[68] In 1992, for the first time, a small cohort was published describing cure in in 11 patients with an orthopedic infection (82%).[69] This study prompted a randomized controlled trial, led by Zimmerli et al., which was published in 1998 and became the most cited article on PJI, reaching >1500 citations.[52] In this study, consisting of 18 patients with PJI and 15 patients with osteosynthesis-associated infection, the effect of ciprofloxacin monotherapy compared to ciprofloxacin with rifampicin was evaluated. Patients were randomized between (a) two weeks of beta-lactam antibiotics followed by ciprofloxacin monotherapy and (b) two weeks of beta-lactam antibiotics with rifampicin (2dd450mg) followed by ciprofloxacin with rifampicin. The rifampicin in the treatment group was started immediately postoperatively. Duration of treatment was 3 months (for hip PJI and osteosynthesis-associated infection) or 6 months (for knee PJI). Dropout occurred in 6 of 18 patients in the rifampicin group (33%). Curation in the rifampicin group was 89%, in the placebo group 60% (intention-to-treat analysis $p=0.10$, per protocol analysis $p<0.02$). This difference in outcome was mostly explained by the development of ciprofloxacin-resistant staphylococci in 4 out of 5 failures in the ciprofloxacin monotherapy group. Unfortunately, the outcome was not stratified for type of infection(PJI versus

osteosynthesis-associated infection) or causative agent (CNS versus *S. aureus*). Also, the study was heavily underpowered although the beneficial effect of rifampicin combination therapy was striking and distinctly different with a few small cohort studies from the 1990s. In those cohort studies the success rate after DAIR for staphylococcal PJI did not exceed 40%.[70 71] In 2020, a second randomized controlled trial was published in which 48 patients with a staphylococcal PJI were randomized between rifampicin combination therapy and beta-lactam monotherapy.[72] Treatment success was comparable in both groups: 72% and 74%. This study was also underpowered, although the study contained three times as much patients as the trial by Zimmerli et al.

Observational cohort studies about PJI:

In many observational studies the role of rifampicin for staphylococcal prosthetic joint infection was evaluated. Since 2005, more than 60 observational studies have been published describing the outcomes of DAIR in staphylococcal prosthetic joint infections, of which less than 30 studies also evaluated the role of rifampicin. Numerous studies, comparing rifampicin combination therapy to a treatment strategy without rifampicin, reported no positive association between rifampicin and treatment success [49 73-79], while other studies showed a positive correlation.[5 80 81] With rifampicin use, success rates are 50-90%, while in patients without rifampicin (described in about ten studies) it varies between 30 and 80%. The cure rate for infected hip prostheses in these studies was in some but not all studies higher than for infected knee prostheses[82]. In addition, in studies in which the use of rifampicin in staphylococcal infections was not described, the cure rate was lower than in the studies in which rifampicin was given.[82] Reported success rates gradually increase over the years, but remain at around 50% in several large cohorts with more than 150 enrolled patients with staphylococcal infections.[83-87] Differences in outcome may be explained by differences in proportion of included polymicrobial PJI, differences in surgical approach, like whether or not mobile parts were exchanged changed during debridement. Different definitions of treatment success are also a relevant factor. The literature regarding the role of rifampicin for staphylococcal PJI has not been systematically appraised yet. The effectivity of antimicrobial monotherapy without rifampicin for staphylococcal or streptococcal PJI has not been evaluated in PJI either. Some observational studies have reported about monotherapy with moxifloxacin, flucloxacillin, or linezolid for staphylococcal PJI, showing reasonable outcomes.[72 73 88 89]

Methodological limitations of observational studies

Selection bias, confounding by indication and survival bias are important methodological limitations of the observational studies discussed here. Selection bias occurs because, due to toxicity and interactions, rifampicin may be less prescribed in vulnerable patients who already have an a priori increased chance of a worse outcome. In addition,

only patients with rifampicin sensitive *S. aureus* are selected for rifampicin treatment. Immortal time bias occurs when rifampicin is withhold in patients until one to two weeks after debridement (after the wound is dry and the sensitivity of the staphylococcus is known). Only patients who do not develop a failure during those two weeks will start with rifampicin, leading to better outcomes in the rifampicin group.[81 90] Confounding by indication can occur because, for example, physicians who prescribe rifampicin are better aware of current guidelines and may also be more skilled surgeons performing who may exchange mobile parts more often during surgery. In most observational studies, the patient characteristics of the groups with and without rifampicin combination therapy were not reported, making correction for these confounders challenging.

Timing and duration of use of rifampicin

To prevent new biofilm formation after debridement by surviving bacteria that attach to the retained implant, rifampicin-combination therapy should be started as soon as possible after surgical debridement. The highly bactericidal activity of rifampicin will rapidly kill any remaining bacteria in the postoperative wound. If surviving bacteria in the postoperative wound attach to the prosthetic joint and cause new biofilm formation, the risk of treatment failure will be high. Therefore, in the very early postoperative period, rifampicin may be mostly needed. Most clinicians however withhold postoperative rifampicin treatment until the wound is dry and the rifampicin sensitivity of the staphylococcus is known. This is due to the presumed risk of selecting for rifampicin-resistant Coagulase-negative skin staphylococci that may secondary infect the implant through the postoperative leaking wound. Although this view is widely accepted, it is not supported by clinical studies that demonstrate relapsing PJI by rifampicin-resistant staphylococcal when administered immediately postoperative. In vitro research shows that rifampicin resistance only develops with in the presence of a high bacterial load and if rifampicin is used as monotherapy. In a patient with a PJI, the bacterial load is significantly reduced during the surgical debridement and patients are always treated with rifampicin combination therapy. In the earlier mentioned RCT of Zimmerli et al. rifampicin was started immediately postoperative, not resulting in rifampicin-resistant staphylococci in patients who failed on therapy[52]. Therefore, it may be justified not to withhold this excellent anti-staphylococcal drug in the early postoperative period in which it may be mostly needed. More data to support this strategy are needed.

The role of chronic suppressive antibiotic therapy

Chronic suppressive antibiotic treatment for PJI is the chronic use of low-dose antibiotics in patients with a (relapsing) PJI who are no longer eligible for surgery or who decide not to undergo further surgery. Chronic suppressive antibiotic therapy is only started after the normal treatment duration for PJI (usually between six and twelve weeks) and is aimed at

f controlling rather than curing the chronic PJI. The rationale behind suppressive therapy is that the persisters within the biofilm that have survived antimicrobial treatment and switch back to a metabolically active state, cannot proliferate further due to a daily rise in antibiotic concentrations. The choice for a certain regimen is dependent on several criteria: (a) the micro-organism is well sensitive to the antibiotic; (b) antibiotics can be taken orally; (c) the safety of long-term use is known; and (d) the antibiotics have a reasonable penetration into bone and joint tissue. The dose of chronic suppressive therapy is usually lower than during conventional antibiotic therapy, because no more tissue infection or osteomyelitis needs to be treated.

Data about the optimal dosing and duration of suppressive antibiotic treatment are absent. Some centers advocate lifelong continuation with suppressive therapy while others state that treatment may be stopped after a two to five years, provided that inflammatory parameters remain low and clinical signs for infection are absent. The treatment strategy and duration for inoperable chronic PJI should always be determined in a multidisciplinary team meeting.

Table 3. Expert-based regimens of antibiotic suppressive therapy used at Leiden University Medical Center

Flucloxacillin 1000mg BD
Doxycyclin 100mg OD
Amoxicillin 1000mg BD
Cotrimoxazol 960mg OD (sometimes lowered further to 480mg OD)
Clindamycin 600mg BD (sometimes lowered further to 300mg BD)

Need for innovative treatment options for PJI

Despite an increasing amount of knowledge about the optimal diagnostic and treatment strategies for PJI, cure rates after treatment remain disappointingly low.[5 6 87]. In several of the largest studies, most closely approximating the real-life clinical situation, cure rates were between 50-70%. This low care rate likely relates to surviving bacteria within a mature biofilm, even after thorough surgical debridement and adequate antimicrobial treatment. Therefore, innovative alternatives for antibiotics, that may act synergistically with antibiotics, are urgently needed. New therapeutic modalities, such as immunotherapy, nanoparticles, bacteriophages, photodynamic therapy, heat induction, novel antibiotics and antimicrobial peptides are several promising complimentary treatment strategies for PJI and need to be tested further.[91 92] In addition, we are in need for in vitro and experimental animal models, that approximate a PJI as much as possible in which the most promising strategies can be further tested in order to enhance future cure rates for PJI.

Outline of the thesis

In the preceding paragraphs, the challenges and knowledge gaps clinicians face when treating patients with PJI have been described. To improve outcome for patients with PJI, high-quality studies are needed to both improve the diagnostic process as well as patient-tailored antimicrobial treatment strategies. As described in this introduction, earlier diagnosis of PJI may enhance success rates. Further, evidence-based antimicrobial treatment strategies are needed for PJI. Lastly, the high rate of relapses after treatment for PJI, even if treated according to the best available level of evidence, urges us to explore novel treatment strategies aimed at eradication of persisters from the biofilm. The current thesis addresses these challenges. The thesis is divided by three parts focused on new diagnostic and antimicrobial strategies.

Part I. The use of E-health to detect prosthetic joint infections

A general introduction to the topic of this thesis is described in **chapter 1**. The *first* part focuses on earlier detection of PJI. A postoperative woundcare app was developed to shorten the time to diagnosis of PJI and to assess the association between postoperative wound leakage and occurrence of PJI. In **chapter 2**, we evaluated the ease of use and perceived usefulness in a group of patients who used the woundcare app in a pilot study. In **chapter 3**, we compared the extent and duration of postoperative wound leakage in patients with and without PJI, using the same smartphone application, in a large multicenter implementation study in The Netherlands.

Part II. Evaluation of current antimicrobial strategies for PJI

The *second* part of this thesis focuses on the evaluation of currently used antimicrobial treatment strategies for staphylococcal PJI. In **chapter 4**, the outcome of PJI in all studies reporting the outcome of staphylococcal PJI after DAIR is assessed in a systematic review and meta-analysis, focused on the use of rifampicin for staphylococcal PJI. In **chapter 4,** we also describe the importance of acknowledging several forms of bias and confounding that are inevitably present in most observational studies about PJI and we discuss how to correctly deal with these. **Chapter 5** specifically focuses on causative micro-organisms and outcome for different surgical strategies for patients with an infected megaprosthesis, a subgroup of patients that is even more challenging to treat compared to PJI after conventional arthroplasty.

Part III. New antimicrobial strategies for PJI

New strategies to combat biofilm-associated infections like PJI are the subject of the *third* part of this thesis. **Chapter 6** describes the results of a large, prospective cohort of

patients with staphylococcal PJI who were treated in our region, according to a predefined protocol, with either a short-term rifampicin strategy or a long-term rifampicin strategy, depending on the hospital patients were admitted to. This large prospective quality registry started after publication of the outcome of staphylococcal PJI treated with DAIR and only short induction therapy with rifampicin is in a small, retrospective observational study ,also described in **chapter 6**. In **chapter 7**, we report on the development of an in vitro biofilm model simulating PJI as much as possible. In this study, the effectivity of several promising anti-biofilm and anti-persister agents was assessed in pretreated mature biofilm models.

Chapter 8 provides a general discussion. The main conclusions of the thesis are highlighted and the implications of our research are put into future perspective.

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