Antimicrobial strategies and multidisciplinary care in prosthetic joint infections

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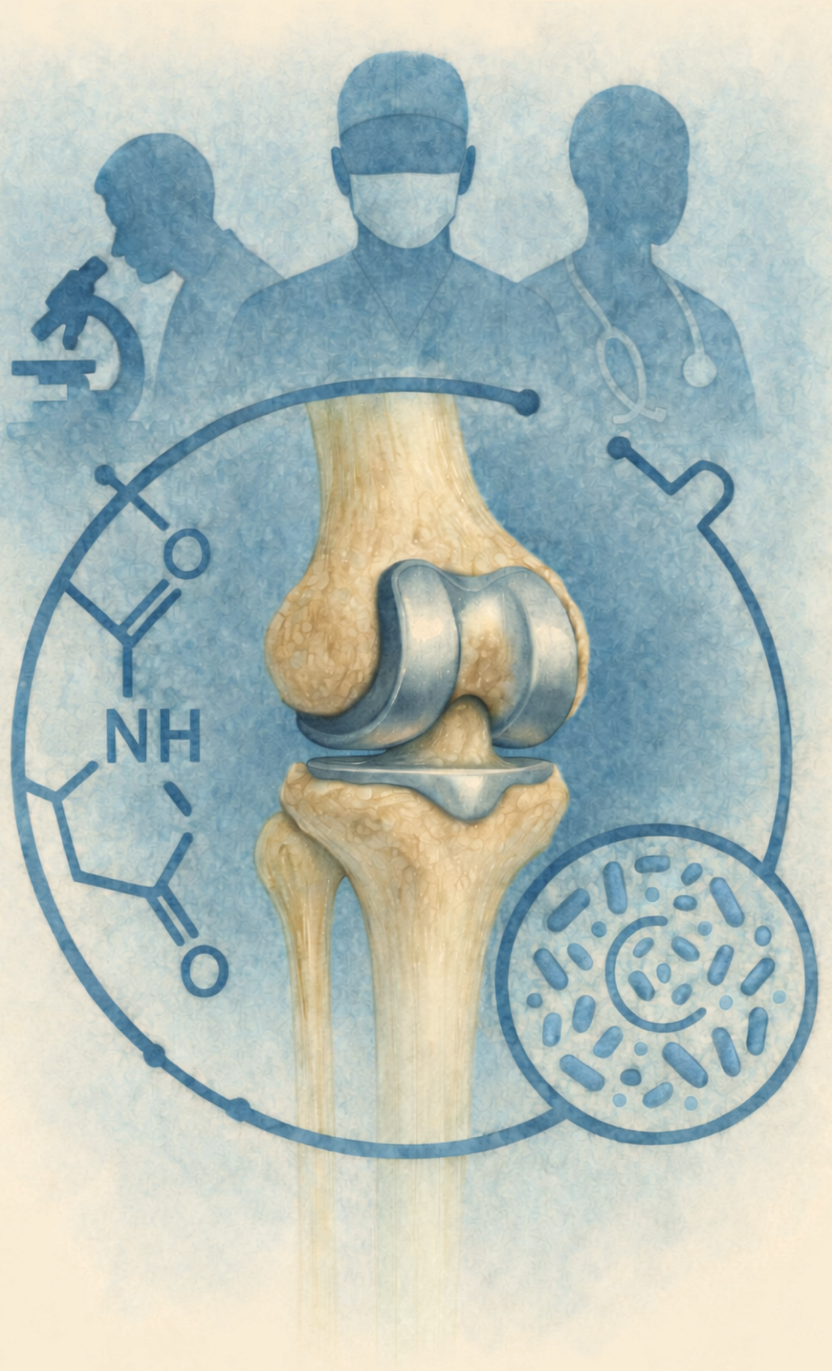
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Chapter 1

Introduction and outline of the thesis

Introduction

Burden of prosthetic joint infections

Prosthetic joint infection (PJI) constitutes one of the most devastating complications of total joint arthroplasty (TJA) and represents a formidable challenge for patients and physicians. It requires extensive surgery combined with prolonged antimicrobial therapy and has a high chance of relapse (1-3). This burdens patients with reduced mobility, loss of autonomy, extended hospitalization(s), toxicity from prolonged antibiotic treatment, and increased mortality over time (4-7). All these factors negatively affect quality of life of patients, both in the short and the long term (7-10). In addition, encountering PJI can weigh heavily on orthopedic surgeons causing guilt, stress and a sense of failure (11, 12).

Moreover, PJI imposes a substantial economic burden on healthcare systems and thus society at large. In 2022 around 800.000 people in the Netherlands were living with a TJA which is one in every 12 persons over 40 years old (13). In the United States of America (US) 770.000 primary TJAs were placed in 2020 and this is predicted to raise to 4.000.000 in 2060 (14). Given a reported incidence of PJI of around 1-2 % in patients with a TJA this led to the annual medical costs of hip and knee PJI in Europe of approximately €350.000.000 and in the US its projected to be a staggering $1.850.000.000 in 2030 (15-17). The total amount for society is even higher because these numbers do not account for indirect costs; for example due to the consequences of patients being (temporarily) unable to work.

In the literature, PJI is also referred to as periprosthetic joint infection, with the latter preferred by some as it more explicitly reflects the involvement of periprosthetic tissues, but both terms denote the same condition. For consistency, the term prosthetic joint infection is used throughout this thesis.

Pathophysiology

During PJI, the bone and surrounding soft tissues are infected, leading to clinical symptoms. These symptoms are caused by an inflammatory process in a response to bacteria, which are also present on the implant surface. Among other bacterial virulence factors, the formation of a microbial biofilm on the surface of an implant makes PJI notoriously difficult to treat (18). Biofilm formation is a dynamic, multi-stage process in which microorganisms adhere to the implant surface and become embedded within a self-produced extracellular polymeric matrix, composed of polysaccharides, proteins, and extracellular DNA, typically measuring up to several hundred micrometers in thickness (19). This matrix acts as a physical and chemical barrier, impeding

the penetration of host immune cells, and creating a unique microenvironment that drives the emergence of a phenotypically distinct subpopulation of bacteria, called persister cells or persisters (20). These cells are characterized by a significant reduction in metabolic activity and cell division, rendering them largely invulnerable to both antibiotics and immune-mediated clearance (20-22). The fundamental difficulty when treating PJI and other biofilm-associated infections is the presence of these persisters. While the immune system supported by antimicrobial therapy can effectively eliminate planktonic bacteria and despite the fact that antibiotics penetrate well into the biofilm (albeit delayed), the persisters will be unaffected (23-26). As long as antibiotic pressure is maintained, persisters remain dormant within the biofilm. Upon cessation of therapy, these cells can revert to their active planktonic phenotype, leading to renewed infection and tissue invasion (Fig 1). Consequently, eradication of biofilm-associated infections such as PJI requires elimination of the persisters embedded in the biofilm. This may be achieved by thorough surgical debridement and cleaning of the implant, but often necessitates its complete removal.

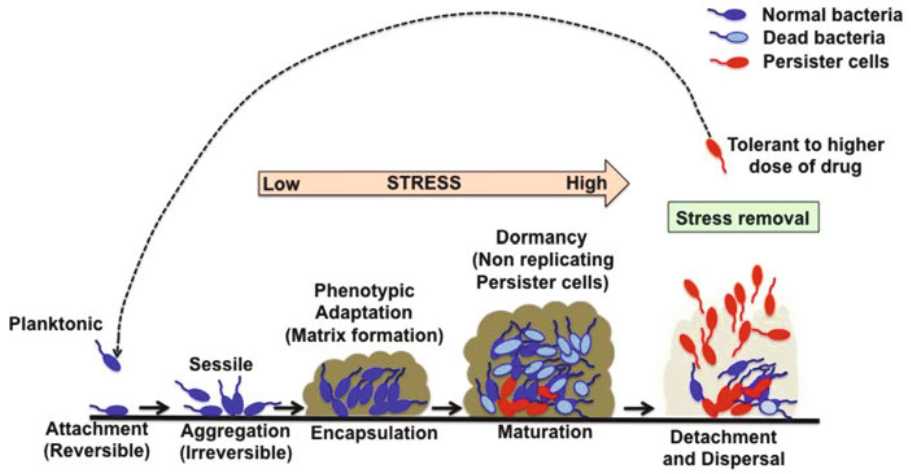

Fig 1. *Planktonic bacteria gradually form a biofilm and switch to persister cells under stress (e.g., antimicrobial therapy). When stress factors are withdrawn the persister cells switch back to active bacteria capable of causing infection. Figure from Alam, A., et al. (2019). Biofilms: A Phenotypic Mechanism of Bacteria Conferring Tolerance Against Stress and Antibiotics: 315–333 (27)*

Clinical presentation

The clinical presentation of PJI can be either acute or chronic. Patients with an acute infection generally have had symptoms for less than 3-4 weeks. Symptoms consist of redness, pain, warmth and (ongoing) wound leakage but rarely fever (3). If this

occurs in the first three weeks to four months after TJA surgery, this is referred to as early acute (postoperative) PJI. Inoculation of bacteria in the joint space is considered to have occurred perioperatively in these cases. *Staphylococcus aureus* and Coagulase negative staphylococci (CNS) are the main species detected in these infections (69-77% combined) followed by streptococci (8-19%), enterococci (9-12%) and Gram-negative bacteria (11-17%) (28, 29). Occurrence of polymicrobial flora of early acute PJI is ranging between 8 and 30% (29, 30). Patients with acute symptoms and who's index surgery has been over 3 months are considered to have late acute PJI, due to hematogenous seeding. These infections are nearly always monomicrobial and mainly caused by *Staphylococcus aureus* (~40%), followed by streptococci (~20%) (31).

A PJI is referred to as being chronic if symptoms occur more than 3 months after the index arthroplasty. Actual inoculation occurred sooner but chronic PJI is typically a low grade infection and it often takes months for symptoms to develop. Patients usually present with non-acute symptoms like chronic pain or a draining sinus tract with or without loosening of the prosthesis (3). If a patient with acute symptoms presents late after start of symptoms, fails on first-line treatment or is treated suboptimal an acute PJI can become chronic. Staphylococci cause the majority of chronic PJI (~65%). The presence of a sinus tract is associated with polymicrobial infections (32, 33).

Surgical treatment options

Since persister cells in biofilms are tolerant to antibiotics, surgical removal of the biofilm is always indicated in PJI (22). The preferred surgical strategy is determined by the clinical presentation and host factors, like the condition of soft tissue and comorbidities. In acute PJI, patients can be managed with the "DAIR"-strategy (34). DAIR stands for Debridement, Antibiotics and Implant Retention. During debridement, the joint is opened, the periprosthetic tissues surgically debrided, the prosthesis thoroughly cleaned (but not removed) and if possible all mobile parts of the arthroplasty replaced (3). The goal of this procedure is to mechanically remove all biofilm from the implant and surrounding tissue. The debridement is followed by long-term antimicrobial therapy (29, 34, 35). By preserving the implant, this approach minimizes surgical morbidity, reduces recovery time, and maintains joint function compared to implant removal or revision surgery (36). Reported success rates of DAIR for acute PJI range from 56% to 90% (37).

Chronic PJI is characterized by a mature biofilm that extends into bone and implant surfaces inaccessible during surgical debridement, creating a larger bacterial burden and more protected niches than in acute infection. This likely explains the poor out-

comes of DAIR in chronic PJI compared with acute cases, with reported success rates below 50% (38). For that reason the preferred treatment for chronic PJI is resection arthroplasty (3). Replacement with a new prosthetic joint can be performed in the same session as the removal (i.e., one-stage revision (1SR)) or in a later stage, ranging 4-12 weeks (i.e., two-stage revision (2SR)). The infection eradication rate following one-stage and two-stage revision surgery is approximately 85% (39). However, completing two-stage revision procedures remains a major challenge, with less than 50% of patients ultimately undergoing reimplantation of the prosthesis (3). Despite advances in surgical techniques and antimicrobial therapy, cure rates for both chronic and acute PJI remain disappointing, particularly when managed with implant retention. This underscores the need to optimize quality of care, not only by improving and tailoring antimicrobial strategies , but also by multidisciplinary collaboration and exploring suppressive antimicrobial strategies that can effectively prevent relapse of PJI with minimal drug toxicity, antibiotic consumption and antimicrobial resistance development. These challenges form the basis of this thesis, which focuses on three key domains of PJI: the role of multidisciplinary teams, targeted antimicrobial strategies of DAIR, and suppressive antimicrobial therapy.

Antimicrobial strategy of DAIR

Antimicrobial therapy is part of any PJI treatment and should be started after surgical intervention and sampling of deep cultures. In case an adequate debridement in acute PJI has been performed (i.e., there is complete removal of the biofilm including persister cells) the goal of antimicrobial treatment is to kill residual planktonic bacteria on the implant and surrounding bone (i.e., osteomyelitis) and soft tissue. Unfortunately, randomized controlled trials (RCTs) on antimicrobial therapy for PJI are scarce and antimicrobial strategies for DAIR vary greatly worldwide (34, 40, 41). In general, following debridement, patients are treated empirically to cover staphylococci (including CNS), streptococci and Gram-negative bacteria in acute postoperative PJI and *Staphylococcus aureus* and streptococci in acute hematogenous PJI. Targeted therapy in Europe consists of 1-2 week of intravenous therapy followed by 10 weeks of oral antibiotics (34, 41, 42). This treatment duration was investigated in the DATIPO trial in which 6 weeks of antibiotics were inferior to 12 weeks in PJI treated with DAIR, 1SR of 2SR (35). In selected cases though, 6 weeks of antibiotic treatment after DAIR can be sufficient (43). This approach for PJI differs from the Infectious Diseases Society of America (IDSA) guideline on PJI treatment, (published in 2013). The IDSA recommends a longer duration of the intravenous phase, often 6 weeks, followed by indefinite oral antibiotics (29, 40, 44, 45). Of note, some (European) authors of this guideline would not treat indefinitely in selected case of staphylococcal or Gram-negative PJI who were treated with rifampicin or fluoroquinolones respectively. Although

the guideline is 12 years old, a recent survey among North-American ID physicians showed that indefinite oral antibiotics is currently still a very common treatment strategy in the US for PJI managed by DAIR (46).

Staphylococcal PJI

Staphylococcal species are the causative pathogen in approximately two-thirds of PJI (47). For staphylococcal PJI managed by DAIR, a combination of rifampicin with a fluoroquinolone (FQ) is widely recommended as the first-line oral antibiotic regimen (40, 42, 48). Rifampicin exhibits potent bactericidal activity against gram positive bacteria, including those residing intracellularly or enclosed within a biofilm matrix (47). Due to rapid development of resistance when given as monotherapy in bacterial infections, rifampicin should be combined with a second antibiotic to prevent this (49). Promising pre-clinical experiments in animal cage models showed an impressive anti-staphylococcal effect on biofilm associated infections and led to the conduct of the first RCT in orthopedic implant-related infections on antimicrobial therapy (48). This 'landmark-trial' by Zimmerli et al. published in 1998 concluded that rifampicin-ciprofloxacin combination therapy in the oral treatment phase was able to cure 100% of included patients with a stable implant and short duration of infection who were managed by debridement followed by three to six months of antibiotics. (50). This publication seemed to confirm the hypothesis that rifampicin combination therapy is superior than other antimicrobial regimens and became widely accepted as first-line therapy for staphylococcal PJI managed with DAIR. Unfortunately, the trial had several serious methodological shortcomings. The study included both PJI and FRI and compared rifampicin-ciprofloxacin combination therapy to ciprofloxacin monotherapy in the oral treatment phase of DAIR. They recruited only 33 patients of which 24 were analyzed for the primary outcome and found a cure rate of 100% in the ciprofloxacin-rifampin group and 58% in the ciprofloxacin-placebo group (per protocol analysis, p=0.02, intention to treat analysis, p=0.10). Currently, such a trial would likely not be performed, as (prolonged) ciprofloxacin monotherapy will be regarded as insufficient therapy readily induces resistance in *Staphylococcus aureus*. The sample size was calculated to include 30 participants, based on an expected low cure rate of 20% in the ciprofloxacin monotherapy group. The trial was terminated prematurely due to treatment failures exclusively occurring in the monotherapy arm, with four out of five relapses (80%) demonstrating ciprofloxacin resistance. Another limitation of this study is the small subset of PJI, comprising 15 of the 33 enrolled patients and the number of PJI analyzed for the primary outcome is not described in the paper. One other RCT has been published on this subject which did not show superiority of rifampicin combination therapy. Karlsen et al. compared beta-lactam or vancomycin monotherapy with rifampicin-based therapy in staphylococcal PJI treated

with DAIR (51). The cure rate in the rifampin combination group was 74% and in the monotherapy group 72%. This trial ended prematurely due toa slow recruitment rate and included 48 patients of the intended 124 in six years' time. Furthermore, both pre-clinical data on rifampicin for staphylococcal biofilm infections and systematic reviews of observational clinical studies on staphylococcal PJI are conflicting (48, 52-55). A recent prospective multicenter cohort study with 200 patients from the Netherlands found no difference in outcome between a rifampicin-based, clindamycin-based or flucloxacillin-based regimen for staphylococcal PJI managed by DAIR (43). Importantly, rifampicin-fluoroquinolone therapy for PJI has a drug discontinuation up to 36% and many clinically relevant drug-drug interactions (56). Notably, as in PJI, rifampicin is recommended in staphylococcal prosthetic valve endocarditis guidelines, despite evidence being limited to observational studies showing no clear benefit and an absence of clinical trials (57). High quality studies are needed to answer the important clinical question whether other (less toxic) antimicrobial strategies than rifampicin-based therapy are equally effective for staphylococcal PJI to facilitate a more patient-tailored approach.

Gram-negative PJI

Gram-negative (GN) bacteria are responsible for 11–22% of PJIs (28, 58). Fluoroquinolones (FQ) are considered as the first-line oral antimicrobial therapy for patients with GN-PJI in most guidelines (40-42). This recommendation is based on the high bioavailability and favorable penetration of FQ into bone and the potential anti-biofilm activity of FQ in pre-clinical studies (59-63). Reported success rates of GN-PJI treated with implant retention and use of FQ range between 66%-94% (31, 64-67). However, clinical evidence supporting the superior effectiveness of FQ over other antimicrobial drugs remains limited, inconclusive and of low methodological quality (31, 64-66, 68-70). There are no RCTs that have investigated antimicrobial treatment of GN-PJI. Moreover, the worldwide rise of FQ-resistant GN infections and the high rates of FQ discontinuation due to adverse effects underscore the necessity of additional effective oral antimicrobial strategies for GN-PJI treated with DAIR (56, 71, 72).

Suppressive antimicrobial treatment

Patients managed with implant retention often receive long-term antibiotics after finishing initial antimicrobial treatment of 6-12 weeks. This strategy is mainly referred to as 'suppressive antimicrobial therapy' (SAT) but some authors prefer 'antibiotic suppressive therapy' (AST) or 'chronic suppression'. As explained earlier, one of the difficulties with achieving cure in PJI is the presence of a biofilm with persisters on the implant. As long as these are not fully removed during the surgical procedure and antibiotic pressure is taken away, persister cells will start to become metabolically

active again and transform to planktonic bacteria that will invade surrounding tissue and cause a clinical relapse.

The use of SAT as part of the antimicrobial treatment plan is common in PJ, ranging from 5-14% in European studies, up to 31% in Australia and up to 87% in US cohorts of patients treated with DAIR (29, 73, 74). Despite this high frequency, there are limited data to guide physicians in clinical practice. The 2013 IDSA guideline on PJI management contains several recommendations on SAT indication, regimen and treatment duration but these are mainly based on expert opinion (40). One of the difficulties when interpreting data on SAT is the absence of uniform indications and lack of clear definitions and concepts. In the US, acute PJI managed by DAIR is often followed by SAT in contrast to Europe where this is not advocated (29, 45, 46, 75). In Europe, SAT is generally reserved for patients who have been treated with no surgery, non-curative surgery (e.g., DAIR for chronic PJI) or have a high chance of relapse (e.g., due the immunosuppression) (33, 76-79). The perception of what is "SAT" differs not only between studies, complicating the comparison of data but also between physicians, potentially obscuring discussions on SAT cases. Unsurprisingly, the reported success rates of SAT vary greatly (between 23% and 95%) and preferred antimicrobial regimens differ around the world (73).

There are scarce data on SAT dosing, with few studies reporting the use of lower than therapeutic dosed SAT (30, 78-80). The IDSA recommends lower dosages for SAT compared to the standard therapeutic dosage for PJI, based on expert opinion (40). Despite this recommendation and the apparent low dosing of SAT in clinical practice, no studies have specifically addressed this issue and investigated different dosing strategies.

If SAT can ever be stopped in PJI is another unresolved clinical problem. The IDSA recommends SAT of indefinite duration and most studies report lifelong continuation of suppression (33, 40, 80, 81). Some authors have reported successful treatment of PJI with SAT when treatment was stopped after one to three years (44, 82-84). It is unknown which indications for SAT permit discontinuing and based on which clinical, biochemical and radiological parameters this decision should be made.

Multidisciplinary approach

Treatment of bone and joint infections (BJI) like PJI is complicated and necessitates collaboration of various medical specialties for optimal outcome. Against the background of an aging patient population with increasing chronic morbidity, polypharmacy, and immunosuppression, multidisciplinary collaboration will become even

more important. Similar to oncology and other medical specialties, a multidisciplinary team (MDT) is generally believed to be beneficial in the care for patients with complex BJI and several orthopedic societies recommend its installment (85-87). In the Netherlands, most hospitals in which patients with PJI are treated already have such teams implemented but in many countries this is not common practice. Since the implementation of such MDTs require both time resources and substantial funding it is important to have an understanding of their quality and effect (88). Current published studies focused mainly on the effect of an MDT on clinical outcome. These observational data suggest that an MDT improves outcomes (89-96). Another aspect of MDTs that has been investigated is the effect on interdisciplinary collaboration, workflow and professional development. Two qualitative studies reported that participants of PJI MDT meetings experienced improved communication and standardization of care after installment of the MDT (97, 98). BJI MDTs may have a similar positive impact on care but more data are needed on other aspects to justify their further deployment. The implementation rate of MDT treatment decisions for example, is a good proxy for effective team-based decision making (99). This has been assessed in many other fields of medicine that make use of MDTs but such an analysis is still lacking for complex BJI MDTs (100-108).

Outline of the thesis

This thesis aims to assess three important aspects of the antimicrobial treatment strategy for patients with a PJI. Considering the complexity of PJI and a growing comorbid population, MDTs are deemed necessary for optimal patient care and are increasingly being implemented. Objective assessment of PJI MDT effectiveness and impact on patient outcome are scarce and much needed. Next, to enable a more patient-tailored treatment and to improve outcome for patient with staphylococcal and GN-PJI treated with DAIR, more effective antimicrobial treatment strategies are needed. Furthermore, the current heterogeneity in the practice of SAT for PJI necessitates the development of uniform strategies and definitions to improve communication between physicians and researchers worldwide. Moreover, studies on optimal SAT dosing and treatment duration are lacking but warranted. This thesis addresses these challenges divided in three parts.

Part I. Evaluating multidisciplinary care for complex bone and joint infections
The first part focuses on the quality and effectiveness of an MDT for PJI and other complex BJI. In **chapter 2** we determined the implementation rate of treatment decisions made by the MDT and analyzed the clinical outcome of patients from which

MDT decisions were not implemented in clinical practice. Additionally, the content and evolution of the team meetings throughout the 7-year study period were assessed.

Part II. Antimicrobial strategies for prosthetic joint infections treated with debridement, antibiotics and implant retention.

The second part of this thesis focuses on antimicrobial strategies for the targeted oral treatment phase of patients with PJI managed by DAIR. In **chapter 3** we describe and discuss our study protocol for the *Rifampicin Combination Therapy versus Targeted Antimicrobial Monotherapy in the Oral Antimicrobial Treatment Phase of Staphylococcal Prosthetic Joint Infection* (RiCOTTA)-trial. This is a currently (2026) recruiting, multicenter, non-inferiority, open-label, randomized controlled trial evaluating monotherapy (i.e., a regimen without rifampicin) versus rifampicin-combination therapy in the oral treatment phase of staphylococcal PJI managed with DAIR. In **chapter 4**, we describe the results of a multicenter, prospective study of patients with Gram-negative PJI who were treated with DAIR. We compared three different targeted antimicrobial regimens: fluoroquinolones, cotrimoxazole and beta-lactams.

Part III. Suppressive antimicrobial therapy for prosthetic joint infections

SAT for PJI is the subject of the third part of this thesis. **Chapter 5** describes the results of a worldwide survey we performed to identify international differences for the most common indications and antimicrobial treatment strategies for SAT. Subsequently, discrepancies to guide the direction of further research were determined. In **chapter 6** we report the outcomes of a systematic review on global SAT practices and propose new definitions of SAT and risk classification for future research. The results of a cohort study that examined if SAT that is lower dosed than therapeutic, is as effective as therapeutically dosed SAT, are presented in **chapter 7.**

A general discussion of the thesis is provided in chapter 8 , including a summary of key findings and discussion of future perspectives.

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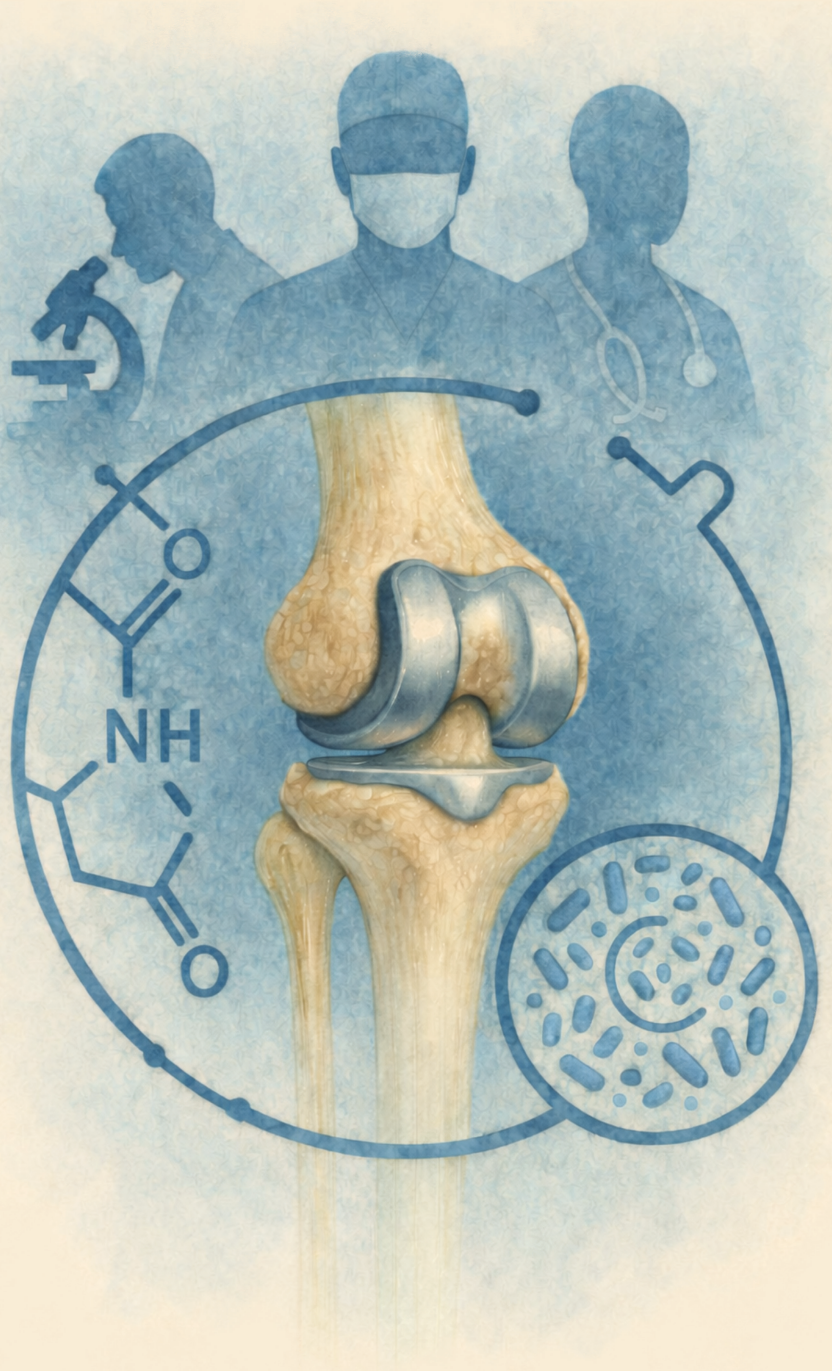
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Part I

Multidisciplinary care for bone and joint infections

Chapter 2

Implementation of multidisciplinary team decisions on the management of complex bone and joint infections: an observational study

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Abstract

Background: Multidisciplinary team (MDT) management of prosthetic joint infections (PJI) and other bone and joint infections (BJI) is increasingly put into practice. However, studies evaluating the performance of MDTs in this field are scarce. We aimed to assess our MDT for complex BJI by determining the implementation rate of team decisions, analyzing factors associated with non-implementation and evaluating the clinical outcome of patients in whom MDT decisions were not implemented.

Methods: An observational study was conducted on all patients with a PJI or other BJI of which the management was discussed during MDT meetings between 2015 and 2022 in a tertiary care academic hospital. Patient characteristics and MDT data were obtained from electronic patient records. The multidisciplinary team consisted of orthopaedic surgeons, trauma surgeons, infectious diseases specialists and clinical microbiologists. A decision was considered not implemented if the patient did not receive the management that was decided by the MDT. Factors possibly associated with non-implementation were statistically analyzed using logistic regression.

Results: The analysis included 1321 MDT decisions on 509 patients. The overall implementation rate of MDT decisions was 92.1%. Reasons for non-implementation were disagreement by the treating surgeon with the MDT regarding the optimal treatment (n=24, 23%), patient preference for a different treatment (n=19, 18%), new clinical information not yet available during the MDT meeting that made the physician change management (n= 17, 16%) or unknown (n=45, 43%). Trauma surgeons were more likely to not implement an MDT decision (odds ratio 2.4, p=0.01) The cure rate of patients who received a different surgical strategy than decided by the MDT was 33%. The cure rate was lower if a patient chose to deviate from the MDT decision (46%) than when the treating physician chose to deviate from the MDT decision (77%).

Conclusion: The implementation rate of decisions made by our complex BJI MDT was high. Furthermore, the current study suggests that non-implementation of MDT decisions on surgical management and non-implementation initiated by the patient lead to poor clinical outcomes. An analysis of MDT decision implementation is a useful tool to evaluate the impact of MDTs and further improve its quality.

Introduction

Prosthetic joint infection (PJI), fracture related infections (FRI) and spinal implant infection (SII) are severe complications after surgery. The surgical and antimicrobial treatment is complex and requires the combined expertise of various medical specialties. Osteomyelitis and septic arthritis of a native joint are also challenging infections to treat. A multidisciplinary team (MDT) approach is considered beneficial in the care for patients with these complex bone and joint infections (BJI). Implementation of an MDT for patients with a PJI or FRI is advocated by several national orthopaedic societies (1-3). The organization of such an approach demands time resources and a considerable financial investment (4). Physicians who participated in PJI MDT meetings experienced that communication and standardization of care improved after installment of an MDT. However, data on the evaluation of quality, effectiveness and impact of MDTs for complex BJI are scarce(5, 6). Observational studies on clinical outcomes of PJI and FRI after implementation of a dedicated MDT report conflicting data and randomized controlled trials have not been performed (7-14). To the best of our knowledge, studies focusing on effective decision making by BJI MDTs are absent. Analysis of the actual implementation of MDT decisions can be a more reliable measure of MDT effectiveness than assessing clinical outcomes only (15). Observational studies in other fields showed that 6-42% of MDT decisions and recommendations were discordant compared to the actual treatment received by patients (15-28). The aim of this study was to evaluate the MDT for complex bone, joint and arthroplasty infections in our hospital by analyzing the implementation of its decisions in clinical management. Furthermore, we analyzed the factors associated with non-implementation and assessed the clinical outcome of patients in whom MDT decisions were not implemented. A secondary objective was to assess the content and evolution of the team meetings throughout the study period.

Materials and methods

This study was conducted at a tertiary care academic hospital in the Netherlands which is specialized in treatment of bone tumours and is a regional referral hospital for PJI and other complex BJI. About 180 arthroplasties are performed on a yearly basis in our hospital of which approximately 30 are tumour endoprostheses. The departments of Infectious Diseases and Clinical Microbiology work in close collaboration with the departments of Orthopaedic and Trauma surgery in case of BJI.

Multidisciplinary Team Meeting

All patients with PJI and other complex BJI are discussed in a weekly MDT meeting, to determine (perioperative) management (e.g. diagnostic procedures, surgical treatment, antibiotic therapy including possible long term suppression, timing of discharge and follow-up). PJI, FRI and SII are discussed at least twice and other complex BJI at least once. Key participants of the team include selected staff members from orthopaedic surgery, trauma surgery, infectious diseases, and clinical microbiology, all with a dedicated interest in BJI. Every meeting is held on the same location and is attended by at least one key member of each medical specialty. The team is complemented by residents from these specialties. Every meeting lasts 30-45 minutes and is prepared, chaired and documented by two orthopaedic surgery residents. The physician running the ward where the patient is admitted or the physician who primarily evaluated the patient in outpatient setting is responsible for enlisting the patient for MDT discussion and selecting the date of the meeting in which the patient will be discussed. All MDT members have access to the electronic patient file system and are expected to prepare enlisted cases prior to the meeting. Only patients who are enlisted beforehand will be discussed. The conclusions and decisions of the MDT are documented in the electronic patient file directly following case discussion. In case of absence of the responsible physician at the meeting, the MDT aims to communicate its decision directly to the physician as well.

Patient population

All cases discussed at the MDT meetings between July 2015 and April 2022 were included. For the purpose of this study, one patient discussed in one meeting was defined as a single MDT record. Data from patients with a PJI were retrieved from a quality register, as described previously (29). For each record, patient demographics, treating medical specialty, diagnosis, microbiology results and therapeutic strategies together with details of the MDT meeting and its decision were extracted from the electronic patient file using CTcue text mining software (CTcue B.V., Amsterdam, The Netherlands) in combination with manual patient file review. Data were stored in a secured database. Records were excluded when the MDT decision was not documented or if follow-up of a referred patient from another hospital was not noted in the electronic patient file of our institution.

MDT characteristics and analysis of decision implementation

MDT decision implementation was specified per medical specialty, type of infection and management category (surgical, antibiotic treatment or diagnostic). A decision was considered not implemented if the patient did not receive the management that was decided on by the MDT. Reasons for non-implementation were divided in four

categories: i. disagreement of the treating physician with the MDT regarding the optimal treatment, ii. patient preference for a different treatment, iii. additional clinical information that became available after the MDT meeting that made the physician change management, iv. the reason was not recorded in the patient file.

Failure was defined as one of the following outcomes: the appearance or persistence of a fistula, unplanned surgical intervention or admission for intravenous antibiotics due to persistence or relapse of the infection, restart of antibiotic treatment in case of relapse after stopping suppressive antibiotic treatment, serious side effects of antibiotic treatment (need for cessation or switch, hospital admission, death) in cases where the patient received antibiotics despite the MDT decision to stop or not initiate, death related to the infection. Patients were considered cured after a follow-up of minimal one year without treatment failure.

The evolution of the MDT meetings was assessed by analyzing the number of discussed patients per meeting, the number of times an individual patient was discussed, the treating medical specialty, the distribution of type of infections and the MDT decision implementation rate over time.

Statistical analysis

Patient characteristics as well as documentation of the MDT meetings were summarized using descriptive statistics. A univariable logistic regression was performed and odds ratios calculated for the assessment of association of categorical variables with non-implementation. P-values ≤0.05 were considered significant. All statistical tests were performed 2-sided (SPSS Statistics for Windows was used (IBM SPSS Statistics for Windows, Version 25.0.0.2, Armonk, NY).

Results

Of 1342 MDT records, 1321 MDT decisions from 329 MDT meetings on 509 individual patients were included. Twenty-one records (1.6%) were excluded due to absence of documentation of the MDT decision or in case there was no follow-up of referred patients from another hospital in the electronic patient file. Baseline clinical characteristics are summarized in Table 1. Forty-four percent of patients had a PJI, 18% (vertebral) osteomyelitis, 16% native joint septic arthritis, 12% FRI, 6% skin and soft tissue infection (SSTI) and 3% SII. A debridement in the context of PJI, SSTI, septic arthritis or osteomyelitis was the most frequently performed surgical treatment (55%). A conservative treatment was chosen in 27% of the patients. The number of

MDT discussions per patient ranged between one and 18; 299 patients (59%) were discussed more than once and 27 patients (5.3%) at seven or more separate meetings. The attendance rate was highest for orthopaedic surgeons, infectious diseases specialists and clinical microbiologists (100%, 100% and 80%, respectively).

Table 1. Characteristics of 509 patients discussed at bone and joint infection multidisciplinary team meetings

Female/Male	214/295
Age, years (IQR)	61 (44-72)
Type of infection (n,%)	
Prosthetic joint infection	219 (44)
Tumour endoprosthesis	89 (18)
Fracture related infection	59 (12)
Spinal implant infection	16 (3)
(Vertebral) osteomyelitis	93 (19)
Septic arthritis native joint	82(16)
Skin and soft tissue infection	31 (6)
Site of infection (n,%)	
Hip	112 (22)
Knee	131 (26)
Other joints	72 (14)
Bone and soft tissue	194 (38)
Treatment strategy(n,%)[a]	
Debridement, Antibiotics, Implant Retention	157 (28)
Debridement of skin and soft tissue infection, osteomyelitis or septic arthritis	153 (27)
One and two stage revisions	47 (8)
Girdlestone resection arthroplasty and amputation	24 (4)
Removal of osteosynthesis material	35 (6)
Non-surgical[b]	153 (27)
Suppressive antibiotic therapy	89 (17)
Number of multidisciplinary team discussions per patient	
1	210 (41)
2-3	179 (35)
4-7	93 (18)
>7	27 (5)

[a]Some patients underwent multiple surgical strategies. A two stage revision counted as one surgery.
[b]Antibiotic therapy only or wait and see policy
Abbreviations: IQR, interquartile range

Implementation and non-implementation of MDT decisions

Out of 1321 MDT decisions, 1216 (92.1%) were implemented and 105 (7.9%) were not implemented. The non-implementation rate of MDT decisions was mostly related to surgical, antibiotic or diagnostic management (n=89, 84.8%). Sixteen (15.2%) decisions concerned a MDT request for follow-up at a future MDT meeting which, for unknown reasons, was not performed.

Non-implementation rates were different between orthopaedic surgery (7.4%), trauma surgery (17.3%) and non-surgical medical specialties (7.5%) (p=0.01). Type of infection, gender and age were not associated with non-implementation (Table 2).

Table 2. Univariable analysis of factors potentially associated with non-implementation of multidisciplinary team decisions

Variables	MDT decisions (n)	Non-implemented decisions (n, %)	OR (95% CI)	p-value[a]
Patient				
Age >65	583	48 (8)	1.0 (0.73 - 1.64)	0.66
Male	742	59 (8)	1.0 (0.67 - 1.50)	0.99
Infection				
Chronic (vs acute)	614	53 (9)	1.2 (0.77 - 1.88)	0.42
Implant related[b] (vs non-implant related)	877	76 (9)	1.36 (0.87 - 2.12)	0.18
Treating specialty				
Orthopaedic surgery	1179	87 (7)	0.59 (0.34 - 1.02)	0.06
Trauma surgery	75	13 (17)	2.4 (1.25 - 4.62)	0.01
Medical[c]	67	5 (8)	0.93 (0.37 - 2.37)	0.88

[a]P-value calculated by chi-squared test

[b]Prosthetic joint infection, fracture related infection, spinal implant infection

[c]Infectious diseases, rheumatology, pediatrics

Abbreviations: OR, odds ratio; CI, confidence interval

The reasons for not implementing MDT decisions are depicted in Figure 1. Non-implementation was mostly due to disagreement of the treating surgeon with the MDT regarding the optimal treatment (n=24, 23%). In 45 cases (43%), the reason could not be deducted from the electronic patient files.

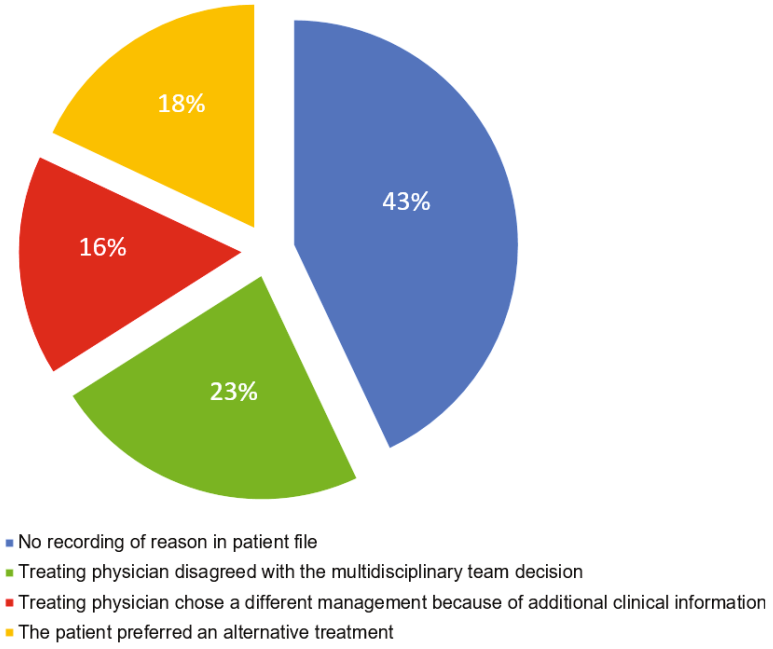

Figure 1. *Reasons of non-implementation of multidisciplinary team decisions for bone and joint infections*

The actual management received by patients and clinical outcome of all patients with non-implemented decisions (n=105) are shown in Table 3 (for a more detailed overview of the deviating strategies, see Supplementary table 1).

Eleven patients in this group (10%) were lost to follow-up and in eight patients (8%) a non-infectious diagnosis was made. Of the remaining 86 patients with a non-implemented decision, 59 (69%) were cured and in 27 patients (31%) the treatment failed. Non-implemented decisions regarding surgical management were associated with a lower cure rate (33%) than non-implemented decisions regarding antibiotic or diagnostic management (cure rates 71% and 83%, respectively). The cure rate was lower in the cases where the patient chose to deviate from the MDT decision (46%) than when the treating physician chose to deviate from the MDT decision (77%).

Table 3. Actual management and clinical outcome of all 105 non-implemented multidisciplinary team decisions

Multidisciplinary team decision	n (%)	Actual management	n (%)	Cure rate[a]
Perform surgery[b]	33 (32)	Non-surgical strategy	27 (26)	33%
		Other surgical strategy	6 (6	
Start/continue antibiotic therapy	32 (31)	No antibiotic therapy	26 (25)	66%
		Other antibiotic therapy	6 (6)	
Stop antibiotic therapy	9 (9)	Antibiotic therapy continued	9 (9)	88%
Perform diagnostic procedure	15 (14)	Imaging not performed	9 (9)	83%[c]
		Punction/biopsy not performed	6 (6)	
Follow-up at future meeting to determine further treatment	16 (15)	No follow-up at future meeting	16 (15)	100%[c]

[a]Cure was defined as the absence of failure with a minimal follow-up of one year. Failure was defined as one of the following outcomes: a fistula, hospital admission due to relapse of the infection, restart of antibiotic treatment after stopping suppressive antibiotic treatment, death related to the infection and side effects of antibiotic treatment leading to discontinuation, hospital admission or death in cases where the patient received antibiotics despite the multidisciplinary team decision to stop.

[b]Debridement, Antibiotics, Implant Retention (DAIR); one stage revision; two stage revision; girdle stone resection arthroplasty; amputation; debridement of osteomyelitis

[c]Excluding eight cases that did not have an infection after final diagnostic work-up

Evolution of MDT meetings

The evolution of the MDT meetings over time is summarized in Table 4. The non-implementation rate of MDT decisions was constant over the seven-year period (range 5.9 – 9.8%, p = 0.78). The mean number of patients discussed by the MDT increased from a of 2.7 to 5.5 per meeting. The mean number of MDT discussions ranged between 2.3 and 2.9 per patient. The majority (90-95%) of patients discussed were treated by orthopaedic surgeons. During the first four years, the percentage of patients treated by trauma surgeons increased from 1% to 11%. During the entire study period the percentage of non-PJI infections increased from 26% to 52%.

Table 4. Characteristics of the multidisciplinary team meeting and the team decision implementation rate

Overall	Overall	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6[a]	Year 7[b]	p-value[c]
General characteristics	*(n)*								
Decisions	1321	121	142	218	192	239	184	225	
MDT meetings	329	45	49	49	50	49	46	41	
New patients	509	51	59	84	73	83	75	84	
Patients discussed per meeting (average)	4.0	2.7	2.9	4.4	3.8	4.9	4.0	5.5	
Treating specialism	*(n,%)*								
Orthopaedic surgery	1179 (89)	116 (96)	132 (93)	202 (93)	173 (90)	196 (82)	164 (89)	196 (87)	
Trauma surgery	75 (6)	1 (1)	1 (1)	3 (1)	6 (3)	26 (11)	13 (7)	25 (11)	
Medical[d]	67 (5)	4 (3)	9 (6)	13 (6)	13 (7)	17 (7)	7 (4)	4 (2)	
Type of infection discussed	*(n,%)*								
Prosthetic joint infection	365 (27)	57 (46)	37 (25)	54 (25)	51 (26)	60 (25)	56 (30)	53 (24)	
Tumour endoprosthesis infection	314 (24)	34 (28)	40 (28)	70 (32)	41 (21)	38 (16)	39 (21)	53 (24)	
Fracture related infection	159 (12)	5 (4)	11 (8)	25 (12)	28 (15)	40 (17)	24 (13)	27 (12)	
Spinal implant infection	35 (3)	4 (3)	0	12 (6)	6 (3)	4 (2)	2 (1)	8 (3)	
(Vertebral) osteomyelitis	237 (18)	15 (12)	32 (21)	25 (12)	36 (19)	42 (17)	44 23)	50 (23)	
Septic arthritis native joint	143 (11)	5 (4)	17 (12)	25 (12)	22 (12)	45 (19)	15 (8)	17 (7)	
Skin and soft tissue infection	51 (4)	1 (1)	7 (5)	5 (2)	9 (5)	10 (4)	4 (2)	17 (7)	
MDT decision implementation	*(%)*								
All specialties	92	92	91	92	93	94	91	90	0.78
Orthopaedic surgery	93	92	90	92	93	95	92	92	0.79
Trauma surgery	83	100	100	67	100	92	85	71	0.36
Medical[d]	93	75	100	100	92	88	100	75	0.38

Table 4. Characteristics of the multidisciplinary team meeting and the team decision implementation rate *(Continued)*

Overall	Year 1		Year 2	Year 3	Year 4	Year 5	Year 6[a]	Year 7[b]	p-value[c]
Type of infection									
Prosthetic joint infection	93	91	92	91	94	93	93	94	
Tumour endoprosthesis infection	93	85	93	93	100	97	87	94	
Fracture related infection	89	100	100	92	96	93	88	69	
Spinal implant infection	83	100	-	75	50	100	100	100	
(Vertebral) osteomyelitis	91	100	87	96	83	93	93	92	
Septic arthritis native joint	94	100	82	100	100	96	100	81	
Skin and soft tissue infection	98	100	100	80	100	100	100	100	

[a]During Coronavirus disease 2019 (COVID-19) pandemic

[b]Contains 10 months of data, June 2021 – April 2022

[c]For trend over time

[d]Infectious diseases, rheumatology, pediatrics

Abbreviation: MDT, multidisciplinary team

Discussion

Multidisciplinary team decision implementation

The current study focused on MDT decision implementation because such an analysis is reported to be a good proxy for effective decision making (15). The high implementation rate of 92.1% confirmed the ability to reach consensus during the MDT. High implementation rates can only be reached when all relevant information is available during the MDT meeting and when the preferences of the patient and treating physician are taken into account. Furthermore, analysis of adherence to MDT decisions allows for a better comparison between BJI MDTs in other clinics than analysis of clinical outcomes because outcome is strongly influenced by the clinical setting (e.g. primary versus tertiary hospital) or the type of infection (e.g. implant-related versus other BJI). The MDT decision implementation rate of our cohort is comparable to other MDT implementation studies in oncology, cardiology, mental health and surgery (4, 15-28, 31-33).

Non-implementation of MDT decisions

The analysis of non-implementation provided us with important insights on the consequences of deviation from MDT decisions. In the group of patients in which the MDT decision was not adhered to, deviating from surgical management resulted in lower cure rates. This could mean that deviating from MDT decisions leads to a worse outcome. However, it is also possible that non-implementation occurs more often in highly complex cases with an a-priori higher risk of failure. Nonetheless, it indicates that an explicit reason should be present to justify an alternative strategy. Of 41 cases, in which the physician clearly documented the reason for a different strategy, new clinical information after the MDT meeting indeed justified the deviation from the MDT decision in 17 cases. This illustrates that 100% MDT decision implementation is not a goal in itself. In a minority of cases, patients themselves opted for a different treatment, probably because their preferences were unknown to the MDT. Patient involvement in the management and evaluation of their infection is important. This may be realized by inviting patients, case managers or dedicated PJI nurses to MDT meetings to bring in more patient centered issues (34). In cancer MDT studies, patients were eager to be more involved, but not all MDT members considered this as beneficial (35, 36). In most cases, the reason to deviate from the MDT decision was not recorded in the patient file. This may be explained by incomplete or improper registration of MDT considerations or unawareness of the physician that the MDT discussed his patient. Unfortunately, we were not able to determine the attendance of individual physicians to the MDT to relate this to non-implementation. Another explanation for the absence of documented considerations in the patient file could be

that the physician did not record this to prevent medicolegal problems of deliberately not implementing MDT decisions (15).

In our cohort, non-implementation of MDT decisions occurred more in patients treated by trauma surgeons. The main reason for this was disagreement by the surgeon with the MDT decision on the treatment strategy. This may be related to the absence of the treating surgeon during MDT meetings. Further, orthopaedic surgeons and infectious diseases specialists were more used to implement MDT decisions because they discussed more patients over the years (Table 2). Cases with a deviation from the MDT recommendation on surgical management had a high failure rate. This points out the need for proper registration of the MDT considerations to inform the physician as much as possible when he considers not to adhere to the MDT decision. The finding of a high failure rate when patients chose a different treatment than the MDT recommended, stresses the importance of informing the patient on the expected outcome when a recommended treatment is not given.

Evolution of the MDT

Over the years, the MDT has expanded its scope from only PJI to a wide range of complex bone and joint infections. This reflects the advantages of our MDT as seen by other specialties that treat patients with complex BJI. Collaboration harmonizes diagnostic and treatment strategies for different BJI, increases the expertise of the participating specialists group and is ultimately beneficial for patients (8-10, 14). The rising number of patients to be discussed, imposes an increased demand for preparation time on MDT participants. In the context of limited time resources prevalent in many healthcare systems, this may negatively influence the quality of decision-making processes. Furthermore, this increase of patients potentially diminishes the available time allocated for in-depth patient discussions. To keep MDT meetings as structured and efficient as possible, we suggest the following measures: i. Development of a clear protocol stating what information is needed at the meeting, how to discuss patients and in which order (facilitated by a strict format in the electron patient file), ii. Collection of complete clinical information when enlisting the patient including the patient's preferences, iii. Thorough case preparation by all team members, iv. Appointment of a chair who adheres to the protocol and strictly keeps track of time (15, 30).

Current and future perspectives

We conducted an appraisal of the available literature to review the indicators that are currently used for assessing the quality and impact of MDTs for BJI. Eight observational studies analyzed clinical parameters before and after installment of an MDT (table 5). The majority reported no statistically significant effect on cure, but this could be due to the small number of included patients (7-14). Inherent to their observational design, these studies are subjected to bias making the true effect of the MDT on outcomes difficult to determine.

Two studies on PJI MDT evaluation focused on MDT member experiences and team dynamics using qualitative methods. After interviewing team members, Awad et al. reported that physicians who participated in MDT meetings experienced that communication and standardization of care improved after installment of an MDT (5). Analysis of video recordings led to the conclusion that MDT meetings increased inter-specialty understanding and communication and improved recognition and acknowledgement of treatment failure (6). To conclude, MDTs for BJI are increasingly being implemented worldwide and are believed to be essential for optimal care, but supporting data are scarce and inconclusive. A randomized controlled trial to answer this question seems unethical due to the widely shared consensus that MDTs improve care for patients (1-3, 10-12, 37). To establish if MDTs are actually beneficial in BJI care we suggest using a broad range of indicators to evaluate its impact. Examples of such indicators are MDT decision implementation, guideline implementation, attendance of team members, documentation of decisions, patient involvement and cost-effectiveness. This will not only provide an insight in local MDT functioning but could also generate suggestions for improvement of MDTs in other clinics where patients with complex BJI are treated.

Strengths and limitations

Major strengths of this study are the large number of included patients and MDT decisions, its longitudinal design and the completeness of the data. This enabled us to comprehensively assess non-implementation considerations after the MDT meetings. Unfortunately, we could not retrieve the time spent per patient discussion, which would provide a more complete insight in the time burden. Further, we did not collect the clinical outcomes of patients who had decisions implemented as this was not the focus of the study. Due to the observational character of the study, we could not evaluate all aspects of the MDT discussions and consultation of patients, for which tape recordings or transcripts of the MDT meetings would be valuable.

Table 5. Cohort studies comparing clinical parameters prior to and after implementation of a multidisciplinary team for complex bone and (prosthetic) joint infections

Reference	Number of cases	Type of infections	Surgical management	Outcomes	Prior to vs after implementation of a multidisciplinary team
Sires et al, 2023	71	PJI	DAIR, 1SR, 2SR, RA	Cure after 2 years	85% vs 86% (p=0.95)
				Length of stay (days)	43.4 vs 42.8 (p=0.94)
				Total number of AB	3.4 vs 2.8 (p=0.19)
				Number of surgeries	1.93 vs 2.25 (p=0.04)
				Percentage DAIR as primary surgery	11.1% vs 34.1%
Rupp et al, 2023	117	FRI	DAIR, 1SR, 2SR	Cure	68% vs 76% (p=0.18)
				Length of stay (days)	52.2 vs 42.3 (p=0.21)
				Bone consolidation	85% vs 90% (p=0.44)
				Recurrence rate within 1 year	27% vs 21% (p=0.24)
Walter et al, 2022	49	PJI	Not given	Success rate	17% vs 65% (p=0.16)
				Recurrence rate within 1 year	41% vs 20% (p=0.12)
				Revision rate	2.5 vs 1.7 (p=0.04)
Vourinen et al, 2021	154	PJI	DAIR, 1SR, 2SR	Cure after 2 years	74% vs 85% (p=0.31)
				Cure of DAIR after 2 years	56% vs 85% (p=0.08)
				Length of stay (days)	49 vs 17 (p=0.00)
				Percentage DAIR as primary surgery	42% vs 90% (p=0.00)
Biddle et al, 2021	58	PJI	DAIR, 1SR, 2SR	Cure after 2 years	59% vs 97% (p=0.00)
				Length of stay (days)	40 vs 47 (p=0.74)
				Time to microbiology advice (days)	8.5 vs 3.1 (p=0.00)
Ntalos et al, 2019	46	PJI	DAIR, 1SR, 2SR	Length of stay (days)	62 vs 29 (p<0.05)
				Number of surgeries (mean)	5.1 vs 1.8 (p<0.05)
				Number of AB (mean)	4.2 vs 2.8 (p<0.05)

Table 5. Cohort studies comparing clinical parameters prior to and after implementation of a multidisciplinary team for complex bone and (prosthetic) joint infections *(Continued)*

Reference	Number of cases	Type of infections	Surgical management	Outcomes	Prior to vs after implementation of a multidisciplinary team
Karczewski et al, 2019	18	PJI	2SR	Recurrence after 2 years	90% vs 97% (p=0.04)
				New infections after 2 years	92 % vs 92% (p=0.95)
				Mean time interval between 2 stages of 2SR (days)	81 vs 67 (p<0.01)
				Length of stay (days)	29 vs 30 (p=0.63)
Bauer et al, 2012	60	BJI including PJI and FRI	Not given	Cure at 6 months	47% vs 57% (p=0.45)
				AB adaptation to microbiology	47% vs 96% (p<0.00)
				Optimal dosing of AB	72% vs 89% (p=0.11)
				Length of stay (days)	19.8 vs 23.1 (p=0.35)

Abbreviations: PJI, prosthetic joint infection; FR, fracture related infection; BJI, bone and joint infection; DAIR, Debridement, Antibiotics, Implant Retention; 1S,: one stage revision; 2SR, two stage revision; RA, resection arthroplasty; AB; antibiotics

Conclusion

In this study, the high implementation rate of MDT decisions on the management of BJI indicated an effective multidisciplinary team. Not implementing MDT decisions on surgical management was associated with a poor clinical outcome. Non-implementation of MDT decisions was mostly the choice of the treating physician and was not always justified. The analysis of non-implementation provided us with several measures to further improve our MDT quality. Analysis of MDT decision implementation is a useful tool for clinicians who wish to evaluate and improve their MDT. Evaluation of different aspects and indicators of MDT performance, other than clinical parameters, will improve the knowledge about providing optimal multidisciplinary care for patients with complex BJI.

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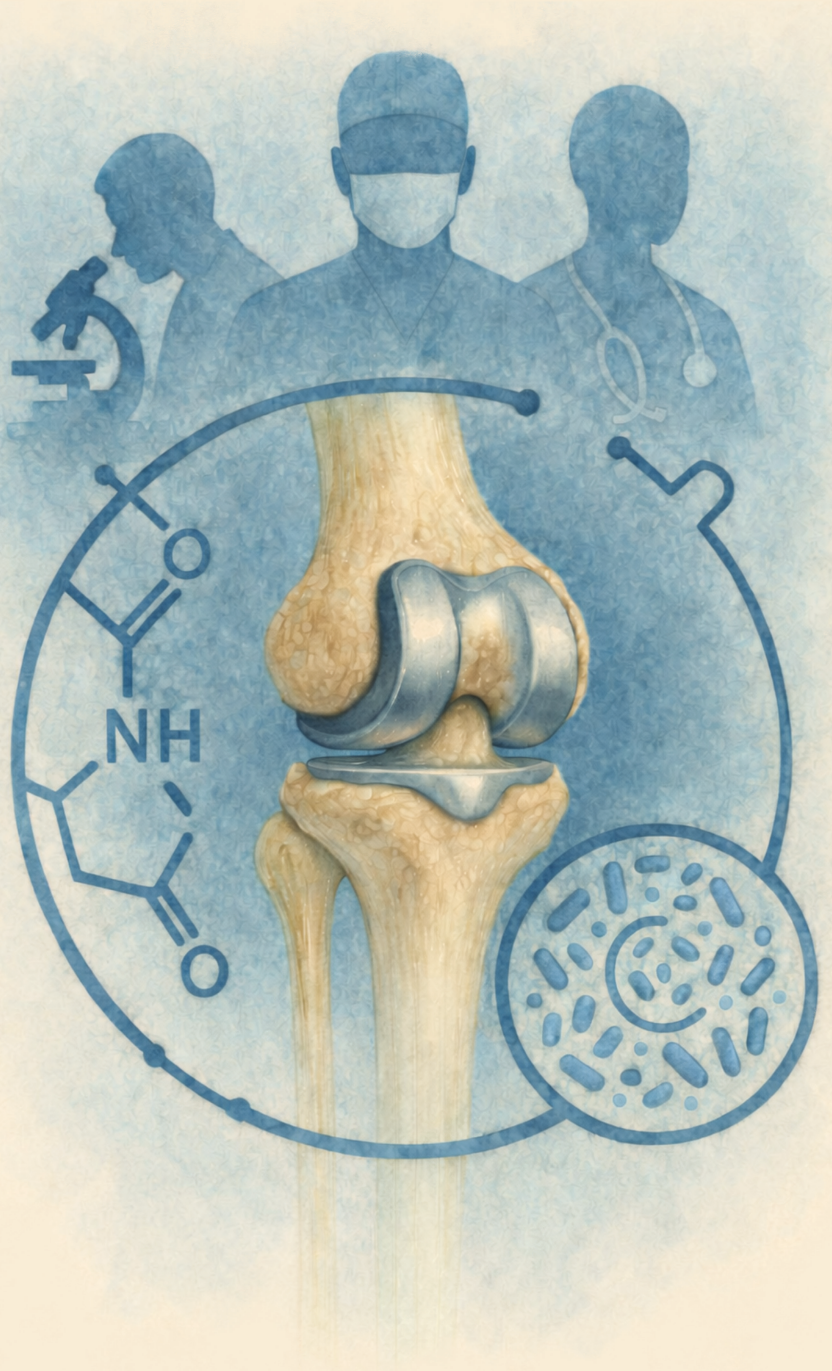
Supplement

Supplementary table 1. Details of the 74 non-implemented multidisciplinary team decisions and actual management regarding surgical strategy and antibiotic treatment

Treatment decision	actual management	cure/failure/lost to follow-up
Surgical strategy		
DAIR, n=7	SAT, n=2	3/4
	AB, n=4	
	No surgery, no AB/SAT, n=1	
One or two stage revision, n=16	DAIR, n=1	3/8/5
	1SR instead of 2SR, n=2	
	Amputation, n=1	
	SAT, n=3	
	AB, n=2	
	No surgery, no AB/SAT n=7	
Remove osteosynthesis material, n=5	Debridement, n=2	2/3
	SAT, n=1	
	AB, n=1	
	No surgery, no AB/SAT n=1	
Amputation, n=2	SAT, n=1	0/2
	AB, n=1	
Debridement of osteomyelitis,	AB, n=1	2/0
n=2	No surgery, no AB/SAT, n=1	
Arthrodesis, n=1	No surgery, no AB/SAT, n=1	1/0
Antibiotic treatment		
SAT, n=24	Not initiated, n=16	16/4/4
	Stopped, n=6	
	Metronidazole instead of fluconazole, n=1	
	Cotrimoxazole instead of ciprofloxacin supp n=1	
AB, n=8	Not initiated, n=4	5/2/1
	Flucloxacillin iv instead of oral, n=2	
	Flucloxacillin instead of vancomycin, n=1	
	Clindamycin instead of flucloxacillin, n=1	
Do not start or stop antibiotic therapy, n=9	SAT, n=5	8/1
	AB, n=4	

[a]sulfamethoxazole/trimethoprim

Abbreviations: DAIR, debridement, antibiotics, implant retention; AB, therapeutic antibiotic therapy; SAT, suppressive antibiotic therapy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Part II

Antimicrobial strategies for prosthetic joint infections treated with debridement, antibiotics and implant retention

Chapter 3

Rifampicin Combination Therapy versus Targeted Antimicrobial Monotherapy in the Oral Antimicrobial Treatment Phase of Staphylococcal Prosthetic Joint Infection (RiCOTTA-trial): protocol for a randomized, controlled, open-label, non-inferiority trial

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Abstract

Background Rifampicin-combination therapy is currently the first-choice oral antimicrobial regimen for staphylococcal prosthetic joint infections (sPJI) treated by debridement, antibiotics and implant retention (DAIR). Lack of high quality evidence to substantiate this recommendation and a high drug discontinuation rate of this regimen warrant investigation of alternative antimicrobial strategies.

Method The *Rifampicin Combination Therapy versus Targeted Antimicrobial Monotherapy in the Oral Antimicrobial Treatment Phase of Staphylococcal Prosthetic Joint Infection* (RiCOTTA)-trial is a multicenter, non-inferiority, open-label, randomized controlled trial evaluating monotherapy (without rifampicin) versus rifampicin-combination therapy in the oral treatment phase of sPJI managed with DAIR. The trial is currently enrolling patients in 18 hospitals. Randomization takes place one to seven days before the switch from intravenous to oral therapy. Total antibiotic treatment duration is 12 weeks and the total follow-up time is 15 months. Eligible patients are adults with knee or hip sPJI managed by DAIR. Primary outcome is treatment success one year after finishing antimicrobial treatment, defined as the absence of: i. PJI related re-surgery, ii. PJI related antibiotic treatment after the initial treatment of 12 weeks, iii. PJI related ongoing use of antibiotics at end of follow-up, iv. Death. Enrolment of 316 patients is needed to confirm non-inferiority of monotherapy with a power of 80%, non-inferiority margin of 10% and based on an estimated treatment success of 85%.

Conclusion Demonstrating non-inferiority of antimicrobial monotherapy during the oral treatment phase of DAIR would enable a more patient-tailored approach when managing sPJI.

Introduction

A prosthetic joint infection (PJI) is a severe complication of orthopedic surgery, occurring in 1-2% of patients with a joint arthroplasty (1). In two-thirds of cases, staphylococci are found to be the causative pathogens (2). Due to the presence of a biofilm, treatment of this infection is challenging and associated with high relapse rate. For acute PJI, cure is often pursued with the strategy of "debridement, antibiotics and implant retention", commonly referred to as DAIR (3-5). Following debridement and one to two weeks of intravenous antibiotics, patients are increasingly being switched to an oral regimen with a total treatment duration of 12 weeks (6, 7).

Guidelines for staphylococcal PJI treated with DAIR recommend rifampicin (rifampin) and fluoroquinolone (FQ) combination therapy as first-line regimen for the oral treatment phase (8, 9). This recommendation is based on data from in vitro studies and foreign body animal models showing strong anti-staphylococcal and biofilm activity of rifampicin (10). These findings are consistent with later observational studies and one (underpowered) randomized control trial (RCT) in which rifampicin ciprofloxacin combination therapy was superior to ciprofloxacin monotherapy in staphylococcal implant-related infections (11-13). In clinical practice, rifampicin is always combined with another antibiotic because resistance against rifampicin can rapidly develop if used as monotherapy (14). Three systematic reviews and meta-analyses reported conflicting results regarding the additional value of the use of rifampicin in the treatment of staphylococcal PJI (15-17).

Unfortunately, the toxicity of rifampicin and FQ combination therapy is a serious impediment when treating patients with PJI. A retrospective cohort study aimed at comparing toxicity of rifampicin-based regimens in staphylococcal PJI showed that unplanned drug discontinuation occurred significantly more often in patients treated with FQ (36%) compared with those in the non-FQ group (3%) (18). Rifampicin is also associated with a range of adverse effects such as drug-induced hepatitis and is a strong inducer of Cytochrome P450 enzymes, leading to clinically relevant interactions with a range of medications (19). Moreover, the European Medicine Agency initiated a program in 2018 to limit unnecessary use of FQ due to rare but serious side effects like irreversible neuropathy, tendon rupture, formation of aortic aneurysms and cardiac arrhythmias (20).

Clinical data about alternatives for rifampicin-based therapy for the oral treatment of PJI are limited. An RCT published in 2020, that included 48 patients with staphylococcal PJI treated with DAIR, aimed to show non-inferiority of oral beta-lactam

monotherapy over rifampicin-based therapy (3). This trial was underpowered because it was terminated before reaching the estimated sample size due to the slow recruitment rate. A recent large prospective cohort study (n=200) evaluated several different antimicrobial strategies for patients with staphylococcal PJI and found comparable effectiveness of clindamycin monotherapy and rifampicin-based therapy (21). Regarding toxicity of clindamycin, its discontinuation was reported to be low (0-9%) in two small retrospective studies investigating clindamycin combination therapy for bone and joint infections (22, 23). These data are important but subject to bias and necessitate an RCT for corroboration.

The limited scientific evidence to support the preference of one antimicrobial strategy over the other together with substantial toxicity associated with the use of rifampicin and FQ warrant the ***R**ifampicin **Co**mbination **T**herapy versus **T**argeted **A**ntimicrobial Monotherapy in the Oral Antimicrobial Treatment Phase of Staphylococcal Prosthetic Joint Infection* (RiCOTTA)-trial. This RCT aims to investigate whether targeted monotherapy is non-inferior to rifampicin-combination therapy in the oral treatment phase of staphylococcal PJI treated with DAIR.

Methods and analysis

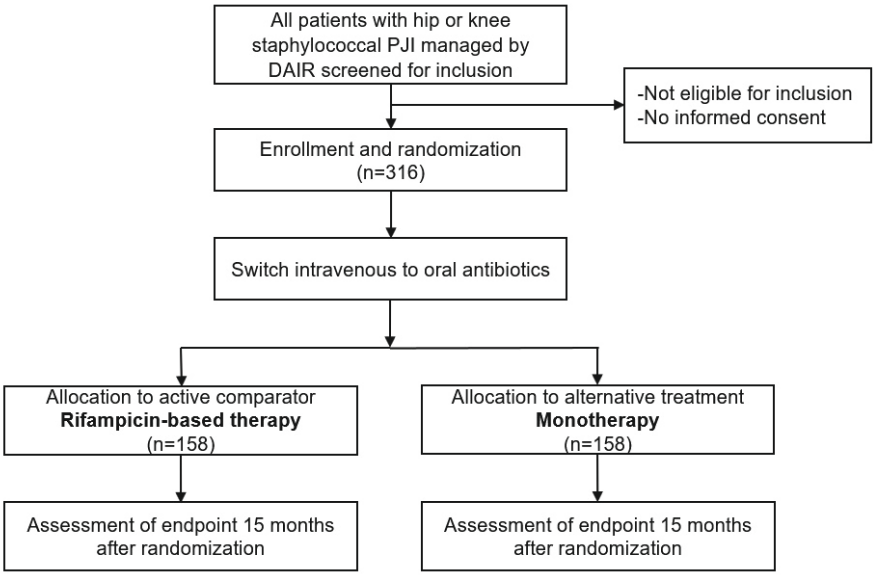

Figure 1. *Flow diagram RiCOTTA-trial design.*

Study design and setting

The RiCOTTA-trial is a multi-center, non-inferiority, open-label RCT conducted in the Netherlands. The trial is currently being carried out in six university medical centers and 12 general hospitals. The first participant was included in May 2023.

Study population

All adult patients diagnosed with a hip or knee PJI that underwent a DAIR procedure whereby the causative micro-organisms are (or include) Staphylococcus species will be screened for inclusion. Patients who do not meet any of the exclusion criteria are eligible for inclusion.

Inclusion criteria

1. 18 years of age or older.
2. Confirmed prosthetic hip or knee joint infection according to the European Bone & Joint Infection Society 2021 definition of PJI (24).
3. The causative micro-organisms are (or include) *Staphylococcus aureus* and/or Coagulase-negative staphylococci.
4. Treatment with DAIR and a planned antibiotic treatment duration of 12 weeks**.**

Exclusion criteria

1. Contra-indication for rifampicin (e.g., resistant strain, proven allergic reaction, difficult drug-drug interactions)
2. Contra-indication for levofloxacin, clindamycin, cotrimoxazole and tetracyclines (e.g., resistant strain, proven allergic reaction, difficult drug-drug interactions)
3. Complicated *Staphylococcus aureus* bacteremia or concurrent endocarditis requiring IV antibiotic treatment > 3 weeks.
4. An infection for which there are no suitable antibiotic choices to permit randomization between the two arms of the trial (e.g., where organisms are only sensitive to intravenous antibiotics)
5. Treatment failure before the start of oral therapy.
6. More than two separate surgical debridements before iv-oral switch.
7. Unsatisfactory response to initial treatment leading to continuation of intravenous therapy beyond day 21.
8. Life expectancy less than 12 months.
9. PJI of a tumor or megaprosthesis.
10. Chemotherapy for malignancy in the next 12 months.
11. Advanced schedule for chronic suppressive antibiotic therapy after the initial 12 weeks.
12. Unlikely to comply with trial requirements following randomization.

13. Pregnancy or breastfeeding.
14. Inability to read or communicate in Dutch or English.

Polymicrobial PJI is not an exclusion criterium per se as long as patients can be randomized between the two treatment arms *and* the possible extra antibiotic needed to treat other micro-organisms is not active against staphylococci. One extra antimicrobial drug (i.e., antibiotic other than the trial medication) is allowed per treatment arm. Including patients with polymicrobial PJI significantly improves generalizability of the outcome of this study.

Trial intervention

Every participant is treated with DAIR with the goal to cure the patient after 12 weeks of antibiotics. Each participating trial site has its own local or regional protocol dictating empirical and targeted therapy during the intravenous (i.e., pre-trial) phase. In all hospitals this phase includes the use of rifampicin, but the timing of onset and duration might differ. When participants switch from intravenous to oral antimicrobial treatment, they will start on the trial medication assigned to them through the randomization process. Block randomization ensures that the various intravenous therapies are equally divided over both study arms. Participants in the rifampicin-based arm will receive a combination of rifampicin 450mg BID and levofloxacin 500mg BID. In contrast, participants in the monotherapy arm will be treated with clindamycin 600mg TID. In case of antimicrobial resistance, antibiotics being out of stock or polymicrobial PJI (when another antibiotic may be needed because it covers all pathogens), alternative antimicrobial regimens will be allowed but only in a strict order to ensure that most patients are treated with the first-choice regimen. Alternatives for levofloxacin in the rifampicin combination arm are (in this order): 1. clindamycin 600 mg TID; 2. Cotrimoxazole 960 mg BID; 3. doxycycline 100 mg BID or minocycline 100mg BID. Alternatives for clindamycin in the monotherapy arm are: 1. Cotrimoxazole 960 mg BID; 2. levofloxacin 500 mg BID; 3. doxycycline 100 mg BID or minocycline 100 mg BID. Ciprofloxacin or moxifloxacin are only allowed in case levofloxacin is out of stock. The total antimicrobial treatment duration is 12 weeks.

Trial recruitment and randomization

Eligible participants are identified during admission or at PJI multidisciplinary team meetings, which are held weekly or bi-weekly in all participating sites. Informed consent is obtained by the local principal investigator (PI) or a delegated person of the local study team. All eligibility criteria will be cross-checked by the central study investigator using an electronic checklist before randomization, which will take place between one to seven days before the planned switch to oral antibiotics. To ensure

comparable frequencies of hip and knee PJI across both study arms and all centers, an independent computer-generated central randomization service (Castor EDC), generates random schedules using permuted blocks, stratified by center and by the anatomical location of the PJI (knee or hip) (25).

Primary outcome

The primary outcome of the trial is treatment success. This is established 15 months after surgical debridement (i.e., one year after finishing antibiotic treatment) and is defined as absence of all of the following:

1. Infection related re-surgery of the index joint.
2. New episode of antibiotic treatment for suspected or proven infection of the index joint after the initial treatment phase of 12 weeks.
3. Ongoing use of antibiotics for the index joint at the end of follow-up.
4. Death by any cause.

Secondary outcome

1. Perceived quality of life during and at the end of antimicrobial treatment using the EQ-5D-5L questionnaire at randomization and 6 and 12 weeks after randomization. The EQ-5D-5L survey is a standardized and validated measure of health status developed by the EuroQol Group to provide a comprehensive generic measure of health for clinical and economic appraisal (26).
2. Antibiotic-associated adverse drug events using the modified Hartwig and Siegel scale (27).
3. Serious adverse events classified by using the fifth version of the Common Terminology Criteria for Adverse Events.
4. The number of patients developing *Clostridioides difficile* infection during treatment.
5. The number of switches to a different oral regimen.
6. Development of rifampicin resistance in patients with a confirmed relapse of staphylococcal PJI.

Follow-up

Follow-up appointments at the outpatient clinic are scheduled for 6 and 12 weeks after the surgical debridement and one year after finishing antimicrobial treatment. During the visit in week 6 and week 12, inflammatory parameters and side effects to antibiotics will be monitored. Serious adverse events will be assessed and reported until end of follow-up at 15 months after debridement. This follow-up schedule aligns with the standard care provided for patients with PJI treated with DAIR in each partic-

ipating hospital. In case of a missed scheduled follow-up visit, the study investigator will contact the participant and/or their general practitioner to identify endpoints. Perceived quality of life is measured at randomization, week 6 of antibiotic treatment and end of antimicrobial treatment (week 12) with an online EQ-5D-5L questionnaire.

Statistical analysis

Sample size calculation and rationale for non-inferiority

The estimated treatment success is 85% at one year after finishing antimicrobial therapy and based on a recent large prospective cohort study with staphylococcal PJI which used the same definition for treatment success (4). We consider monotherapy not inferior to rifampicin-combination therapy when the difference in cure rate will be less than 10%. Considering this success rate and minimal loss to follow-up, 316 participants are needed to prove non-inferiority with 5% one-sided alpha and power of 80%. The reason for a 10% non-inferiority margin lies in the potentially large clinical advantage of demonstrating a similar success rate for treatment with less toxicity and drug-drug interactions. Therefore, the non-inferiority margin may be larger than in studies in which, for instance, differences in mortality are investigated. The 10% margin was determined after balancing the potential risks and benefits of the two treatment strategies. The same margin was used in recently published non-inferiority trials in infectious diseases: the DATIPO-trial on antimicrobial treatment duration in PJI, and the POET-trial on oral treatment for endocarditis (6, 7, 28).

Primary outcome

As the recommended approach in non-inferiority trials, the hypothesis of non-inferiority will be tested in a per-protocol analysis. This analysis will include only patients for whom treatment completely complied with the allocated antimicrobial regimen (plus or minus seven days of alternative treatment). Non-inferiority will be confirmed if the upper bound of the 90% one-sided confidence interval for the difference in absolute risks of treatment success between rifampicin-based therapy and monotherapy is below the non-inferiority margin of 10%. An additional analysis will be performed, accounting for death unrelated to PJI as a competing risk. For the primary outcome we will also perform an intention-to-treat analysis, which will include all randomized patients regardless of changes of treatment. There are no prespecified subgroup analyses planned.

Secondary outcome

All statistical comparisons of the secondary outcome will be performed in both the intention-to-treat and the per protocol study population. Health-related quality of life

(EQ-5D-5L results) will be analyzed using Analysis of covariance (ANCOVA) test per timepoint. The number of serious adverse events, all antibiotic associated adverse events, number of antibiotic regimens switches, number of *Clostridioides difficile* infections during treatment and occurrence of rifampicin resistance in participants with a relapse will be compared by Chi-square tests.

Benefit and risks assessment

The main risk of this study would be a higher failure rate in the monotherapy arm. However, a clinically relevant difference in outcome between the two study arms is not expected. This is based on both a recent RCT that showed non-inferiority of monotherapy and a large prospective study in which monotherapy was as effective as rifampicin-based regimens for staphylococcal PJI (3, 4).

A risk of a higher failure rate should be weighed against the advantages if monotherapy will be as effective as rifampicin-based therapy: more treatment options to ensure a more patient-tailored approach, potentially less side effects and decreased pill burden,, less drug-drug interactions and a narrower antibiotic spectrum.

Monitoring and data management

The RiCOTTA-trial will be monitored by a Data Safety and Monitoring Board (DSMB) composed of a clinical PJI expert, an epidemiologist and a clinical statistician, to ensure the safety and conduct of this study. They will evaluate all relapses for their possible relation with the given treatment and inform investigators in case of differences between the two arms. Interim analysis will be performed after 50% of the planned number of participants have completed follow-up or when 50% of expected failures have occurred. The DSMB will have access to data and interim results and may recommend early closure of the trial if, in their judgment, interim evidence is sufficiently strong that one of the treatment arms is clearly indicated or contraindicated. In case of premature termination, recruitment of participants will be stopped, and the interim results will be used for publication of the trial.

Data collection is performed by trained members of the study team and will be handled in compliance with the General Data Protection Regulation (EU) 2016/679. Only data that are necessary to assess the outcomes of the trial are gathered. All data are encrypted and anonymized using an identification number and stored in an electronic Case Report Form on an online database (Castor EDC) (25). All identifiable information is kept at the local study site where the participant is being treated. The central study coordinators record the anonymized data. The entire study dataset will

be available to the central study team while local PIs only have access to data from individuals enrolled at their own research site.

Ethics and dissemination

Ethical approval was acquired from the Medical Ethics Review Board Leiden, The Hague, Delft (the Netherlands) and is applicable to all participating study sites. The Declaration of Helsinki, the Note for Guidance on Good Clinical Practice (ICH GCP; CPMP/ICH/135/95, step 5 consolidated guideline) and the EU Clinical Trial Regulation (536/2014) are followed during the trial (29). The trial is registered in Clinical Trials Information System (CTIS) with EU trial number 2022-501620-26-00 and registered on clinicaltrials.gov with ID number NCT06172010.

The results of the primary study will be published in a peer reviewed journal. Upon completion of the trial and publication of the primary manuscript, data requests may be directed to the researchers at the Leiden University Center for Infectious Diseases, located at the Leiden University Medical Center.

As per 22nd of April 2025, 66 patients are enrolled in the trial.

Discussion

Currently, there is no high quality evidence to guide the antimicrobial treatment of staphylococcal PJI treated with DAIR. Nonetheless, rifampicin-based therapy is considered first-line therapy despite conflicting results from pre-clinical experiments, systematic reviews based on observational studies and two underpowered RCTs (4, 8, 9, 11-13, 15-17, 30). The benefit of proving that oral monotherapy (i.e., an oral antimicrobial strategy without the use of rifampicin) has comparable efficacy as rifampicin-based therapy lies in the possibility for physicians to offer a more patient-tailored approach. Such an approach is much needed since there is a high drug discontinuation with rifampicin-FQ regimens and rifampicin has many clinically relevant drug-drug interactions (18). Additionally, monotherapy will have a less broad antibiotic spectrum, potentially decreased pill burden and less toxicity (23, 31). These benefits will have such a big impact on clinical practice that they are the main reason and justification of the RiCOTTA-trial. Since current data suggest that monotherapy is not less effective than (but not superior to) rifampicin-based therapy, a non-inferiority design is most appropriate for answering the main research question.

The only two previous RCTs on this topic were hampered by important methodological shortcomings. Zimmerli et al investigated implant-related staphylococcal infections in which they compared rifampicin-ciprofloxacin combination therapy to ciprofloxacin monotherapy (11). At present, a trial with such an intervention would not be conducted, because longstanding treatment with ciprofloxacin can easily induce resistance in *Staphylococcus aureus,* as also occurred in this trial.(32, 33). The calculated sample size of only 30 participants was based on a low anticipated cure rate (20%) in the ciprofloxacin arm. The trial was terminated prematurely, because all failures occurred in the monotherapy arm and four out of five relapses (80%) had developed resistance to ciprofloxacin. A second limitation of this study is the relatively small number of PJIs: 15 of the 33 included patients.

The trial conducted by Karlsen et al. compared beta-lactam or vancomycin monotherapy with rifampicin-based therapy in staphylococcal PJI treated with DAIR (3). They recruited patients for six years at five study sites but could only include 48 patients of the intended 124. Slow enrolment is a well-recognized challenge when setting up RCTs for PJI management (34). With the design and management of the RiCOTTA-trial, we focused on several aspects that could potentially improve enrolment of patients (figure 2).

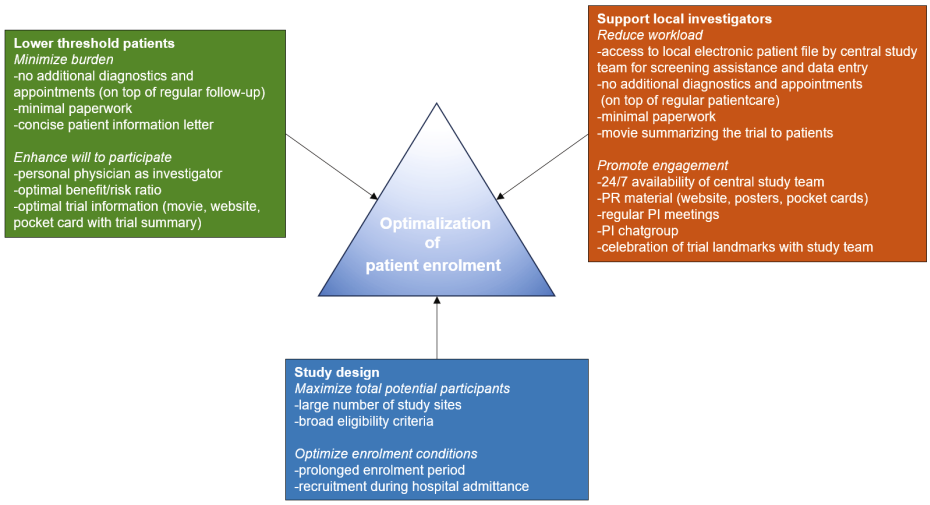

Figure 2. *Components of RiCOTTA-trial design and conduct to optimize patient enrolment. PI: principal investigator; PR: public relations*

First of all, to increase the total number of eligible patients, we are performing this study with a large number of high volume arthroplasty centers (n=19) and formulated broad eligibility criteria. Next, the enrollment period is long (one to three weeks) which provides ample time for both investigators to recruit potential participants and patients to consider participation whilst still admitted. Further, we aimed to create a low threshold for patients to participate in the trial by fully aligning the protocol with the care they will receive regardless of participation (i.e., participants do not undergo additional investigative procedures on top of the standard care for PJI except three short online questionnaires). Patients are informed and recruited by their attending physicians instead of a health care provider unknown to them (e.g., from an external clinical research organization) (35). Finally, the motivation of local PIs is a key aspect of multicenter trial screening and patient enrolment. Since all PIs are physicians who have to invest time in the RiCOTTA-trial on top of regular working hours, we reduced their workload and promoted engagement with the following measures:

- Support from central study coordinators with screening and data entry (by having digital access to electronic patient files of all study sites)
- Creation of a study website with information for both patients and investigators (https://www.protheseinfectie.nl/studie-informatie-ricotta-studie);
- Distribution of trial posters and information pocket cards to local study sites;
- 24/7 availability of central study coordinator;
- Organization of PI meetings twice of year, wherein trial progress and difficulties are discussed with all study sites;
- Celebration of trial landmarks with study team;
- A movie explaining the trial and summarizing the subject information sheet to patients was produced which can easily be shown on phone or laptop, saving the PI time

The choice of the specific antimicrobial regimen in the monotherapyarm is a crucial and challenging aspect of the RiCOTTA-trial and similar RCTs. As stated above, in the trial by Zimmerli et al, monotherapy with ciprofloxacin resulted in (an expected) high failure rate and calculation of a small sample size. Available data suggest that both oral beta-lactams and clindamycin have comparable effectiveness as rifampicin-based therapy (3, 4). The choice for clindamycin (over oral beta-lactams) as main comparatorwas made because of its good bio-availability, bone penetration and in vitro action against *Staphylococcus aureus* (32, 36). Furthermore, most study investigators (all physicians with extensive experience treating PJI) had more experience using clindamycin than oral beta-lactams in bone and joint infections, which was also taken into account when reaching consensus on trial design. Last, a recent,

large prospective observational study in which well-defined monotherapy treatment strategies for staphylococcal PJI were evaluated reported clindamycin as most effective alternative treatment option for staphylococcal PJI (4). We chose rifampicin-FQ combination therapy as active comparator arm because this is widely recommended as first-line therapy for staphylococcal PJI managed by DAIR and there is little data on rifampicin-clindamycin combination therapy. Recent studies also suggest, that., if rifampicin was used, fluoroquinolones appeared to be the most effective companion drug (37). To maximize recruitment rate and generalizability of the study outcome, alternative antibiotics are allowed in both study arms, but only when clindamycin or FQ is contraindicated (e.g., clindamycin resistance). This advantage was carefully weighed against its negative effect on study validity. Alternatives are allowed because the main goal of the RiCOTTA-trial is to prove non-inferiority of monotherapy (i.e. a regimen not based on rifampicin).

Allowing every site to provide their standard of care during the intravenous (i.e., pre-trial) treatment phase, improves feasibility of the study but should be taken into account when assessing the final outcomes. The study sites differ in their choice of empirical and targeted therapy during this phase but they all include rifampicin. Only the timing of onset and treatment duration of rifampicin varies. Most sites start when the wound is dry and do not stop rifampicin. Other sites start directly postoperative and treat with rifampicin for five days. Therefore, when the non-inferiority hypothesis of the current study is confirmed, this does not imply that rifampicin should be entirely withheld from patients with staphylococcal PJI managed by DAIR. It only indicates that antimicrobial monotherapy (i.e., non-rifampicin regimen) in the oral treatment phase is not worse than rifampicin combination therapy.

An obvious limitation of the study is the lack of blinding of study participants, study investigators and healthcare professionals, due to the rifampicin-induced (harmless) orange discoloration of body fluids. Earlier studies have used riboflavin to mimic the colorization of rifampicin (11, 38). We did not opt for this method because the primary study endpoints are objective and therefore not expected to be influenced by knowing to which group a study participant is randomized. Moreover, use of placebo would increase the pill burden in the monotherapy arm. This could impact the quality of life of participants, which is a secondary outcome of this trial. Lastly, the outcomes of this trial could be less generalizable to parts of the world with high clindamycin resistance among staphylococcal PJI. On the other hand the outcome of participants treated with alternative monotherapy regimens will also provide data that can aid in clinical practice.

Conclusion

Demonstrating non-inferiority of monotherapy (i.e., a regimen without rifampicin) will allow physicians to adopt a more patient-tailored approach when considering antibiotics for patients during the oral treatment phase of staphylococcal PJI managed by DAIR.

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Chapter 4

Targeted oral antimicrobial regimens for Gram-negative prosthetic joint infections: a prospective multicenter study

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Abstract

Objectives: Fluoroquinolones (FQ) are considered the most effective antimicrobial treatment for Gram-negative prosthetic joint infections (GN-PJI). Alternatives are needed due to increasing FQ resistance and side effects. We aimed to compare different targeted antimicrobial strategies for GN-PJI managed by debridement, antibiotics and implant retention (DAIR) or one-stage revision surgery (1SR) and to review the literature of oral treatment options for GN-PJI.

Methods: In this prospective, multicenter, registry-based study, all consecutive patients with a PJI caused by a GN microorganism (including mixed infections with Gram-positive microorganisms), managed with DAIR or 1SR from 2015 to 2020, were included. Minimum follow-up was one year. Patients received targeted therapy with either oral FQ, oral cotrimoxazole or with intravenous or oral β-lactams. Survival analysis was performed with use of Kaplan-Meier and Cox proportional hazards models to identify factors potentially associated with treatment failure.

Results: Seventy-four patients were included who received either FQ (n=47, 64%), cotrimoxazole (n=13, 18%) or β-lactams (n=14, 18%). Surgical strategy consisted of DAIR (n=72) or 1SR (n=2). Median follow-up was 449 days (interquartile range 89–738 days). Failure free survival did not differ between the FQ (72%) and cotrimoxazole (92%) groups (log rank, p=0.13). This outcome did not change when excluding all pseudomonal PJI in the FQ group.

Conclusions: Cotrimoxazole is a potential effective targeted antimicrobial therapy for patients with GN-PJI. A randomized controlled trial is needed to confirm the findings of this study.

Introduction

Gram-negative (GN) bacteria are the causative pathogen in 11-22% of prosthetic joint infections (PJI) (1, 2). Treatment with fluoroquinolones (FQ) is recommended as the first-line (oral) antimicrobial therapy for patients with GN-PJI (3-6). This recommendation is based on the high biological availability and good diffusion of FQ into bone and synovial fluid and the presumed anti-biofilm activity of FQ extrapolated from results of several in vitro models (7-11). However, clinical studies on the effectiveness of FQ for PJI are scarce, of low quality, and heterogeneous with respect to outcome (12-19). Furthermore, the global emergence of FQ resistant GN-PJI and the high discontinuation rate of FQ in patients with PJI due to side-effects necessitate other effective (oral) antimicrobial treatment strategies (16, 20, 21).

Cotrimoxazole could be an effective alternative to FQ because of good bone diffusion and high biological availability, yet clinical data on the use of cotrimoxazole for GN-PJI is nearly absent (11, 14, 18, 19, 22). Therapy with β-lactam antibiotics for GN-PJI was as effective as oral FQ in one small study (14).

In 2015, five hospitals in the Netherlands specialized in PJI care coordinated their protocols for the treatment of PJI and set up a prospective register to evaluate their management of PJI. The protocol regarded both FQ and cotrimoxazole as equally suitable first-line therapy for the oral treatment phase for GN-PJI taken into account both effectivity and antimicrobial stewardship: cotrimoxazole has a higher threshold for development of resistance than FQ. In the protocol, β-lactams were considered a second-line option. In this prospective study we aimed to compare the effectiveness of these antimicrobial strategies for patients with GN-PJI treated with debridement, antibiotics and implant retention (DAIR) or one-stage revision surgery (1SR).

Patients and methods

Ethics

The study was approved by the institutional review board of Leiden University Medical Center with a waiver of written informed consent and conducted according to Dutch law and regulations regarding medical research. All patients were informed by their treating physician about the registry and were included unless they chose to opt out.

Study Design

This is a multicenter, prospective, registry-based observational study. The quality registry entailed five regional hospitals in the south-west of the Netherlands that harmonized treatment for patients with PJI, as described in a previous publication (23). The treatment protocol was drafted by all participating physicians before start of data collection. In every participating center, a multidisciplinary team (MDT), consisting of orthopedic surgeons, infectious diseases physicians and/or clinical microbiologists, discussed treatment decisions and protocol deviations on a weekly basis. Data were stored in a secured online database.

Data Collection and Treatment Protocol

All adult patients diagnosed with a GN-PJI between January 1, 2015 and November 3, 2020 were eligible for inclusion. Patients treated with DAIR or 1SR were included to focus on the effectiveness of antimicrobial therapy in patients with a newly placed or retained implant while patients treated with two-stage revision or resection arthroplasty were excluded. Patients with polymicrobial PJI were not excluded. The diagnostic and surgical procedures were standardized in all centers. Perioperative cultures were obtained prior to the start of empiric antimicrobial therapy which consisted of flucloxacillin in acute PJI or vancomycin in chronic PJI. In case of DAIR, empiric GN coverage with an aminoglycoside (or ceftazidime in case of a contra-indication for aminoglycosides) was added for a maximum of 48 hours awaiting Gram-stain and definitive cultures. Targeted therapy against GN bacteria consisted of one to two weeks of intravenous (IV) β-lactam antibiotics followed by four to 11 weeks of monotherapy with oral ciprofloxacin or levofloxacin 500 mg twice-daily or oral cotrimoxazole 960 mg (trimethoprim 160 mg / sulfamethoxazole 800 mg)twice-daily. In case of resistance or side effects, patients were treated with β-lactams for the entire treatment duration. The decision to treat with either FQ or cotrimoxazole was always made by the MDT; the considerations for this choice were not collected in the database.

Definitions

PJI was defined as recommended by the 2013 Infectious Diseases Society of America (IDSA) guideline on PJI (3). The main outcome was treatment failure which was defined as: I. Surgical debridement after antimicrobial treatment had ended, II. Removal of the prosthesis III. Start of suppressive antimicrobial therapy, IV. Death attributable to PJI.

PJIs were classified as either: early postoperative (less than one month after initial surgery), chronic (symptoms more than three weeks and diagnosis more than one month after surgery) and acute hematogenous (symptoms less than three weeks in a previously asymptomatic patient).

Patients were stratified in to one of three targeted treatment strategies: FQ, cotrimoxazole or β-lactam. Patients in the FQ and cotrimoxazole group were treated for at least 50% of the treatment duration with oral FQ or oral cotrimoxazole, respectively. Patients in the β-lactam group received a β-lactam for the entire treatment duration (IV only or IV followed by oral therapy).

Statistical Analysis

Baseline clinical characteristics were summarized using descriptive statistics. To compare differences between antimicrobial strategies chi-square test or Fishers exact test (in case *one or more expected values are less than 5*) was used for categorical variables and one-way analysis of variance or Kruskal Wallis tests for continuous variables. To compare failure free survival between groups (counting from the day of DAIR or 1SR), Kaplan-Meier estimates were performed. Patients were censored at the time of death if the cause was not attributable to PJI. A Cox proportional hazards regression model was used to determine the association of baseline characteristics and antimicrobial strategy with treatment failure. Survival SPSS Statistics for Windows was used (IBM SPSS Statistics for Windows, Version 29.0.0, Armonk, NY).

Results

Seventy-four patients were included in the study (Figure 1).

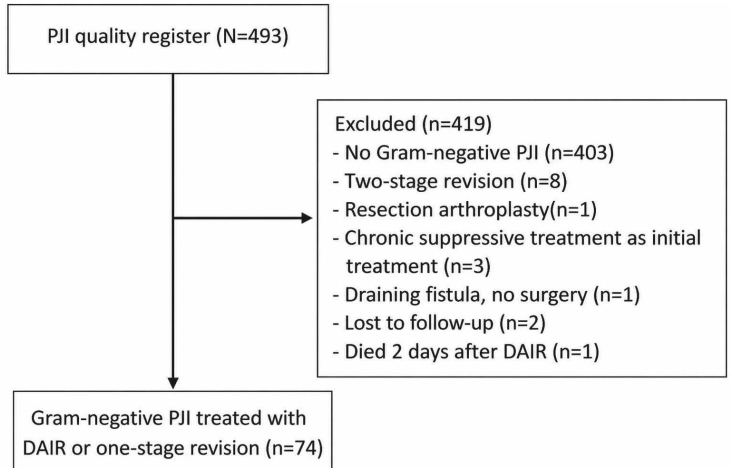

Figure 1. *Inclusion flowchart.*
PJI: prosthetic joint infection; DAIR: debridement, antibiotics and implant retention

Clinical characteristics of all patients and stratified per antimicrobial strategy are summarized in table 1. The majority of patients had a hip PJI and 57% of the infections was polymicrobial. Three patients (4%) had FQ-resistant GN microorganisms and were treated with cotrimoxazole (n=1) or β-lactams (n=2). Patients in the β-lactam group had more chronic infections, tumor endoprostheses, polymicrobial infections, pseudomonal infections and coinfections with enterococcal species compared to the other two groups.

Table 1. Baseline characteristics of cohort of Gram negative prosthetic joint infections, stratified per antimicrobial strategy

	All n=74	Fluoroquinolones n=47	Cotrimoxazole n=13	β-lactams n=14
General characteristics				
Male sex (%)	31 (42)	22 (47)	4 (31)	5 (36)
Age, years (mean, SD)	70 (12)	69 (13)	74 (9)	71 (11)
Joint				
Hip	55 (74)	37 (79)	8 (61)	10 (71)
Knee	17 (23)	10 (21)	4 (31)	3 (21)
Upper limb	2 (3)	0	1 (8)	1 (7)
Revised implant[a]	17 (23)	11 (23)	2 (15)	4 (29)
Tumor endoprosthesis	8 (11)	4 (9)	1 (8)	3 (21)
Previous PJI[b]	5 (7)	2 (4)	1 (8)	2 (14)
Comorbidities				
Diabetes Mellitus, n (%)	18 (24)	13 (28)	2 (15)	3 (21)
Chronic kidney disease (eGFR <60mL/min)	11 (15)	4 (9)	4 (31)	3 (21)
Rheumatoid arthritis	3 (4)	0	2 (15)	1 (7)
Immunosuppressants	7 (10)	4 (9)	2 (15)	1 (7)
Malignancy	10 (14)	4 (9)	2 (15)	4 (29)
Reported smoking (n=42)	15 (36)	11 (23)	2 (15)	2 (14)
Body mass index (median, IQR)	30 (26–34)	30 (28–35)	26 (25–30)	30 (24–34)
Clinical presentation				
Fistula	2 (3)	1 (2)	0	1 (7)
C-reactive protein (median, range)	54 (17–210)	68 (21–241)	42 (13–226)	42 (15–173)
Bacteremia	6 (8)	4 (9)	1 (8)	1 (7)
Timing infection				
Early postoperative (<3 weeks)	42 (57)	28 (60)	7 (54)	7 (50)
Acute hematogenous	26 (35)	17 (36)	5 (38)	4 (29)
Chronic PJI (>3 weeks symptoms)	6 (8)	2 (4)	1 (8)	3 (21)
Days from first symptoms to surgery (median, IQR)	5 (3–9)	4 (2–8)	6 (4–24)	8 (3–15)

Table 1. Baseline characteristics of cohort of Gram negative prosthetic joint infections, stratified per antimicrobial strategy *(Continued)*

	All n=74	Fluoroquinolones n=47	Cotrimoxazole n=13	β-lactams n=14
Microbiology, n (%)				
Escherichia coli	18 (24)	9 (19)	3 (23)	6 (43)
Enterobacter species	18 (24)	14 (30)	4 (31)	0
Pseudomonas aeruginosa	14 (19)	10 (21)	0	4 (29)
Proteus species	16 (22)	10 (21)	0	6 (43)
Klebsiella species	14 (19)	6 (13)	4 (31)	4 (29)
Other Gram-negative[a] Fluoroquinolone resistance	11 (15) 3 (4)	7 (15) -	4 (31) 1 (8)	- 2 (14)
Polymicrobial PJI	42 (57)	26 (55)	6 (46)	10 (71)
+ staphylococci	25 (34)	15 (32)	4 (31)	6 (43)
+ enterococci	17 (23)	6 (13)	3 (23)	8 (57)
+ streptococci	10 (14)	7 (15)	2 (15)	0

Abbreviations: SD, standard deviation; PJI, prosthetic joint infection; eGFR, estimated glomerular filtration; IQR, interquartile range;

[a]Minimum of 1 revision surgery of the same implant as the current PJI. [b]Minimum of 1 previous infection of the same implant as the current PJI.

Data on treatment, follow-up and outcome are shown in Table 2. Median follow-up time was 449 days (interquartile range (IQR) 89–738 days). The raw success rates were 69% (51/74) for the entire cohort, 72% (34/47) in the FQ group, 92% (12/13) in the cotrimoxazole group and 36% (3/14) in the β-lactam group. The median duration of antimicrobial treatment was 64 days (IQR 42–87 days) in the FQ group, 57 days (IQR 41–101 days) in the cotrimoxazole group and 42 days (IQR 19–65 days) in the β-lactam group, including patients who failed during therapy. Patients in the β-lactam group underwent a re-DAIR more often and received empirical GN antimicrobial therapy less often than patient in the FQ and cotrimoxazole group. In the β-lactam group, five patients were switched to oral therapy and nine received IV antibiotics for the entire treatment duration. None of the patients were treated with combination therapy for GN pathogens during the targeted antimicrobial phase.

Table 2. Treatment characteristics and outcome stratified per antimicrobial strategy

	All n=74	Fluoroquinolones n=47	Cotrimoxazole n=13	β-lactams n=14	P value
Days of follow-up (median, IQR)	449 (89–738)	446 (90–738)	473 (368–736)	98 (20–797)	
Surgical treatment strategy (n, %)					
DAIR	73 (97)	47 (100)	11 (85)	14 (100)	
RE-DAIR needed	38 (51)	24 (51)	4 (31)	10 (71)	0.08[a]
One-stage revision procedure	2 (3)	0	2 (15)	0	
Empirical antimicrobial Gram-negative coverage	48 (65)	33 (70)	11 (85)	4 (29)	<0.01[a]
Days of antimicrobial treatment[c] (median, IQR)	56 (42–88)	64 (42–87)	57 (43–101)	42 (19–65)	0.08[b]
Intravenous	15 (10–24)	14 (9–24)	15 (9–20)	17 (14–44)	
Oral	44 (34–71)	47 (34–70)	47 (42–86)	35 (19–66)	
Failure	23 (31)	13 (28)	1 (8)	11 (64)	<0.01[a]
Days to failure (median, range)	42 (8–535)	69 (8–275)	365	33 (14–535)	

Abbreviations: DAIR, Debridement, Antibiotics, Implant Retention; IQR, interquartile range;
[a]Calculated with Fisher exact test. [b]Calculated with Kruskal Wallis test. [c]including failed patients.

Figure 2 shows the survival curves for both the cotrimoxazole and the FQ group which did not differ statistically significant (log rank, p=0.13). This outcome did not change when excluding all pseudomonal PJI from the analysis (log rank, p=0.14). The β-lactam group was not included in this analysis because it differed too much in baseline characteristics with the FQ and cotrimoxazole groups.

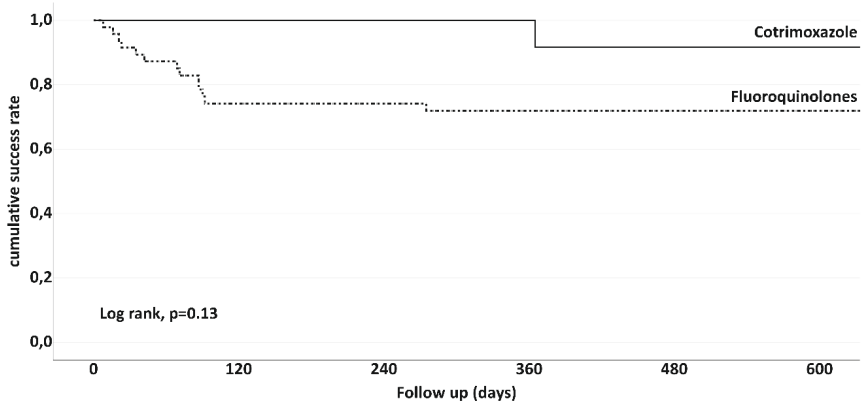

Figure 2. *Survival analysis for Gram-negative prosthetic joint infections treated with DAIR or one-stage revision, related to antimicrobial treatment strategy.*

The presence of a tumor endoprosthesis, not receiving empirical GN antimicrobial coverage, and coinfection with enterococci were associated with failure in univariable analysis (Table 3). Multivariable analysis was not performed due to the small number of patients in the cotrimoxazole and β-lactams groups.

Table 3. Univariable analysis of clinical characteristics possibly associated with failure

	Failure n (%)	Univariable analysis HR (95% CI)	P value
Patient factors			
Age >70	10 (26)	0.67 (0.29–1.54)	0.35
Smoker	7 (47)	0.82 (0.52–1.28)	0.38
On Immunosuppressants	1 (14)	0.40 (0.05–2.98)	0.37
Diabetes mellitus	4 (22)	0.56 (0.19–1.65)	0.29
Implant type			
Knee (vs hip and upper limb)	7 (41)	1.53 (0.63–3.71)	0.35
Previous PJI[a]	2 (40)	1.69 (0.40–7.23)	0.48
Revised implant[b]	7 (41)	1.74 (0.71–4.23)	0.22
Tumour endoprosthesis	5 (63)	3.10 (1.14–8.47)	0.03

Table 3. Univariable analysis of clinical characteristics possibly associated with failure *(Continued)*

	Failure n (%)	Univariable analysis HR (95% CI)	P value
Microbiology			
Pseudomonas aeruginosa	7 (50)	2.35 (0.97–5.73)	0.06
Enterococcus species coinfection	9 (53)	2.51 (1.08–5.82)	0.03
Polymicrobial infection	16 (38)	1.87 (0.77–4.54)	0.17
Treatment			
>7days between first symptoms to _surgery	6 (24)	0.68 (0.27–1.71)	0.41
No empirical treatment covering _Gram-negative microorganisms	12 (46)	2.60 (1.12–6.01)	0.03

The abbreviations used in the table are as follows: HR - hazard ratio; CI - confidence interval; PJ – prosthetic joint infection.

[a]Minimum of 1 previous infection of the same implant as the current PJI. [b]Minimum of 1 revision surgery of the same implant as the current PJI

Discussion

In this prospective multicenter study, patients with GN-PJI who received targeted oral antimicrobial monotherapy with cotrimoxazole after DAIR or 1SR had similar outcomes as patients who received FQ, although numbers were small. The overall success rate of 69% is in line with other observational studies on GN-PJI who reported success rates between 64% and 86% (15, 17, 19, 22). To the best of our knowledge, this is the first study that compared specific oral antimicrobial strategies for GN-PJI.

Fluoroquinolones

The cure rate of 72% with targeted monotherapy with FQ in our cohort is comparable to other reported success rates of FQ for GN-PJI (14, 15, 19). FQ are the most studied oral antibiotics in bone and joint infections (BJI) and most clinical studies date from the 1980s and 90s and were focused on osteomyelitis (24-26). High biological availability and good bone penetration made FQ an attractive oral alternative to IV therapy (27). Two randomized trials on the oral treatment of GN osteomyelitis compared oral ciprofloxacin with IV antimicrobial therapy. In the first trial by Greenberg *et al.* (n=30) treatment was successful in 10/14 patients (71%) on ciprofloxacin and in 15/16 patients (94%) on IV antibiotics (not specified) (28). In the second trial by Gentry *et al.* (n=59) oral ciprofloxacin (success rate 77%) was as effective as IV β-lactams with or without aminoglycosides (success rate 79%) (29). Three observational studies, of patients with GN osteomyelitis treated with oral FQ, reported outcomes that were similar to these two trials (24-26). To best of our knowledge, randomized controlled

trial data comparing different oral antimicrobial strategies for the treatment of GN osteomyelitis are absent.

Data from in vitro experiments and foreign body animal models on the effect of different antibiotics on GN microorganisms favor FQ over cotrimoxazole in *Escherichia coli and Stenotrophomonas maltophilia* biofilms and FQ over β-lactams in *Pseudomonas aeruginosa* biofilms (7-10). The IDSA 2013 guideline recommendation of oral ciprofloxacin for GN-PJI was based on expert opinion and two small observational studies reporting success rates of 80% (in five patients with GN-PJI treated with cefepime-FQ combination) and 80% (in 47 patients with GN-PJI treated with DAIR and ciprofloxacin) (4, 18, 30). Since 2013, seven additional cohort studies were published that analyzed the antimicrobial treatment of GN-PJI (Table 4). Rodriguez-Pardo *et al.* (n=174) concluded that the use of FQ was protective against failure in GN-PJI treated with DAIR (hazard ratio (HR) 0.22, 95% confidence interval (CI) 0.13–0.37) (19). Tornero *et al.* (n=62) reported that antimicrobial regimens not containing FQ were strongly associated with failure (odds ratio 6.5, 95%CI 1.8–23.8) (31). Both studies compared any FQ use (monotherapy with FQ and combination therapy containing FQ) with all other antimicrobial regimens that did not contain FQ. It is likely that confounding by indication and immortal time bias influenced outcomes in these studies (32). Further, the findings of these two studies were not confirmed by Fantoni *et al.* (n=82), Wouthuyzen-Bakker *et al.* (GN-PJI, n=48), and Papadoupolos *et al.* (n=131) who did not report an association between the use of FQ and improved outcome in GN-PJI (13, 16, 17). To date, only Grossi *et al.* (n=76) compared two different antimicrobial regimens for GN-PJI: oral FQ preceded by IV β-lactams was as effective as an entire course of IV β-lactams without FQ (HR 0.73 95%CI 0.19–2.77) (14). However, in this study, the majority of patients in both the oral FQ group (51/58, 88%) and the IV β-lactam group (11/18, 61%) received combination therapy, often with cotrimoxazole, making the effectiveness of monotherapy with FQ and β-lactams difficult to assess.

Table 4. Observational studies reporting on the effects of oral antimicrobial treatment on the outcome of Gram-negative prosthetic joint infections

Reference	Number of GN cases	Population	Surgical management	Variable	Outcome
Martinez-Pastor *et al.* 2010	7	ESBL+ GN PJI	DAIR		*Success rate*
				monotherapy: cotrimoxazole (n=4)	75%
Aboltins *et al.* 2011	17	PJI	DAIR followed by chronic suppression		*Success rate*
				monotherapy: ciprofloxacin (n=12)	92%
				amoxicillin/clavulanic acid (n=3)	67%
				ciprofloxacin + amoxicillin/clavulanic acid (n=2)	100%
Jaen *et al.* 2012	47	PJI	DAIR		*Success rate*
				any use fluoroquinolone[a] (n=35) vs no fluoroquinolone (n=12)	69% vs 58%, p=0.25[c]
				monotherapy: fluoroquinolone (n=28)	82%
Rodriguez-Pardo *et al.*[e] 2014	173	PJI	DAIR		*Association with failure*
				any use of ciprofloxacin (n=124)	HR 0.22 (0.13–0.37) p<0.00[b]
					Success rate
				any use ciprofloxacin[a]	79%
				any use of cotrimoxazole[a] (n=10)	50%
Tornero *et al.* 2014	62	PJI	DAIR		*Association with failure*
				no fluoroquinolone (n=14)	OR 6.5 (1.8-23.8), p=0.01[f]
Grossi *et al.*[d] 2016	76	PJI	DAIR, 1SR, 2SR		*Association with failure*
				no fluoroquinolone (n=18)	HR 0.75 (0.21 – 2.63) p=0.65[b]
					Success rate
				monotherapy: fluoroquinolone (n=7)	71%
				any use of fluoroquinolone[a] (n=58)	78%
				any use of cotrimoxazole[a] (n=19)	84%

Table 4. Observational studies reporting on the effects of oral antimicrobial treatment on the outcome of Gram-negative prosthetic joint infections *(Continued)*

Reference	Number of GN cases	Population	Surgical management	Variable	Outcome
Tornero *et al.* 2016	21	PJI	DAIR		*Success rate*
				any use of fluoroquinolone[a] (n=19) vs monotherapy: cotrimoxazole (n=2)	94% vs 0%, p=0.01[c]
Wouthuyzen-Bakker *et al.* 2019	48	Late acute PJI	DAIR		*Success rate*
				fluoroquinolone (n=35) vs no fluoroquinolone (n=13)	66% vs 62%, p=0.79[c]
Papadoupolos *et al.* 2019	131	MDR and XDR	DAIR, 1SR, 2SR, RA		*Success rate*
		PJI			No effect on outcome (data not provided in publication)
Fantoni *et al.* 2019	82	PJI	DAIR, 1SR, 2SR, RA	fluoroquinolone (n=not provided)	*Association with failure*
					HR 0.73 (0.19–2.77) p=0.64[b]
Hanssen *et al.* 2024	74	PJI	DAIR, 1SR	monotherapy: fluoroquinolone (n=47) vs cotrimoxazole (n=13)	72% vs 92%
					p=0.13

Abbreviations: PJI, prosthetic joint infection; DAIR, Debridement, Antibiotics, Implant Retention; 1S,: one-stage revision; 2SR, two stage revision; RA, resection arthroplasty; HR, hazard ratio; MDR, multidrug resistant; XDR, extensively drug resistant; OR, odds ratio; SMX-TMP, sulfamethoxazole/trimethoprim; ESBL, extend spectrum beta-lactamase. [a]All antimicrobial regimens containing this drug, including combination therapy [b]Cox regression; [c]Chi square test; [d]Most antibiotic treatment regimens in this study consisted of combination therapy; [e]24 patients from this study were also included in the study of *Jaen et al.* from 2012; [f]Logistic regression; [g]Fisher Exact test

Taking all these data into consideration, it is not certain if FQ are the most effective antimicrobials for GN-PJI. In addition to this equipoise, several reasons necessitate the search for effective alternative strategies, most importantly the rising incidence of FQ resistant GN infections, also in PJI (16, 33). Second, the European Medicine Agency initiated a program in 2019 to limit the use of FQ due to serious side effects which may arise like irreversible neuropathy, tendon rupture and the formation and rupture of aortic aneurysms. Lastly, drug adherence to FQ in combination with other drugs can be problematic: unplanned drug discontinuation occurred in 36% of patients on rifamycin with FQ compared to 3% of patients on rifamycin without FQ in patients with staphylococcal PJI (20). FQ monotherapy is reported to be well tolerated with a <4% discontinuation rate(34).

Cotrimoxazole

Twelve of 13 patients (92%) in our study were successfully treated with oral cotrimoxazole after two weeks of IV β-lactams. This high success rate compared to FQ could not be explained by the absence of *Pseudomonas aeruginosa* infections. Good bone penetration and high biological availability make cotrimoxazole a drug of interest for treating BJI (11). However, clinical data that inform on cotrimoxazole for BJI are limited and derived mainly from observational studies on staphylococcal infections, of which two included PJI (35-39). Stein *et al.* successfully treated 11 of 20 patient (55%) with multi drug resistant staphylococcal PJI managed with implant retention or revision surgery between 1989 and 1997 (39). Deconinck *et al.* reported a success rate of 71% in 28 patients with PJI treated with cotrimoxazole. All patients in this study were treated with a combination of two or more antibiotics and 47% of the infections were caused by a GN microorganism but outcome of GN-PJI was not provided (36).

The outcome of GN-PJI treated with cotrimoxazole is mentioned in four other small case series with a combined success rate of 69% in 35 patients, but most of these patients received double or even triple therapy, often with FQ or β-lactams (14, 19, 22, 40). Possible explanations for the lesser use of cotrimoxazole are feared toxicity and the reported inferiority of cotrimoxazole compared to FQ in in vitro biofilm and foreign body animal models (8, 10). With respect to side effects, cotrimoxazole had to be discontinued due to side effects in only 6–18% of patients in BJI cohorts (36-37). Still, possible bone marrow and renal toxicity, skin disorder and drug-drug interactions, should be taken into account when prescribing this drug, especially in the elderly PJI population.

β-lactam antibiotics

Patients in our study who were treated with β-lactams had a high failure rate of 64% and median time to failure was 50% shorter compared to patients who were treated with FQ. This poor outcome might be explained by the overrepresentation of risk factors for failure in the β-lactam group: chronic PJI, no empirical antimicrobial coverage for the causative GN microorganism, pseudomonal infections, enterococcal co-infections, polymicrobial PJI and more re-DAIRS. However, this could not be statistically analyzed due to the small sample size of this group. Unfavorable clinical findings could have led to a continuation of the IV therapy with β-lactams instead of switching to an oral regimen with cotrimoxazole or FQ resulting in selection bias of more high-risk patients in the β-lactam group. Low biological availability of β-lactams might also explain the poor outcome in patients who were switched to an oral β-lactam. In the aforementioned study of Grossi *et al.*, IV β-lactams were equally effective as FQ for GN-PJI, yet the majority of patients were treated with combination therapy and only seven patients received monotherapy IV β-lactams (14). Therefore, given the paucity and bias of the available data, it is not possible yet to provide evidence based recommendations for or against β-lactam monotherapy for GN-PJI.

Strengths and limitations

Strengths of this study are its prospective design and the clearly defined monotherapy strategies. This approach is less prone to bias than studies in which one antimicrobial strategy (e.g. all regimens containing FQ, including combination therapies) is compared with all other treatments combined (e.g. all regimens not containing FQ). The disadvantage of combining several strategies in one group is the risk of wrongfully rejecting a possibly effective strategy within that combined group. It is difficult to assess the effectiveness of a single drug when combination therapies are included.

Our study was limited by the small group of patients treated with cotrimoxazole and β-lactams and larger studies are obviously needed to confirm our findings. Second, the study population was heterogeneous due to the inclusion of patients with polymicrobial PJI and chronic PJI, but these are also patient groups for whom data are needed to inform clinicians about the most optimal treatment. The study was designed to include both patients treated with DAIR and 1SR but due to the low number of 1SR (n=2) the results cannot be extrapolated to this treatment strategy. Thirdly, the considerations for the choice for either FQ or cotrimoxazole were not recorded, so confounding by indication cannot be excluded. With the exception of the absence of pseudomonal PJI in the cotrimoxazole group, baseline characteristics were not different between cotrimoxazole and FQ and both strategies were equally divided

over the participating centers. Lastly, the database does not contain information on side-effects, so the safety of the three strategies could not be assessed.

Conclusions

Current recommendations for the treatment of GN-PJI are based on in vitro models, experimental foreign body animal models and limited conflicting clinical data. The data from this study suggest that cotrimoxazole is a promising antimicrobial treatment option for GN-PJI in selected patients but its safety and effectivity compared to FQ need be determined in larger observational studies and, ideally, a randomized controlled trial.

Acknowledgments
We are grateful to Josefien Hessels and Maxime Gerritsen who had an important role in importing patient data into the Castor database. We also acknowledge the support from local research coordinators Menno Benard, Jantsje Pasma, Bregje Thomassen, and Marjolein Schager for their help during the setup and follow up of the quality registry.

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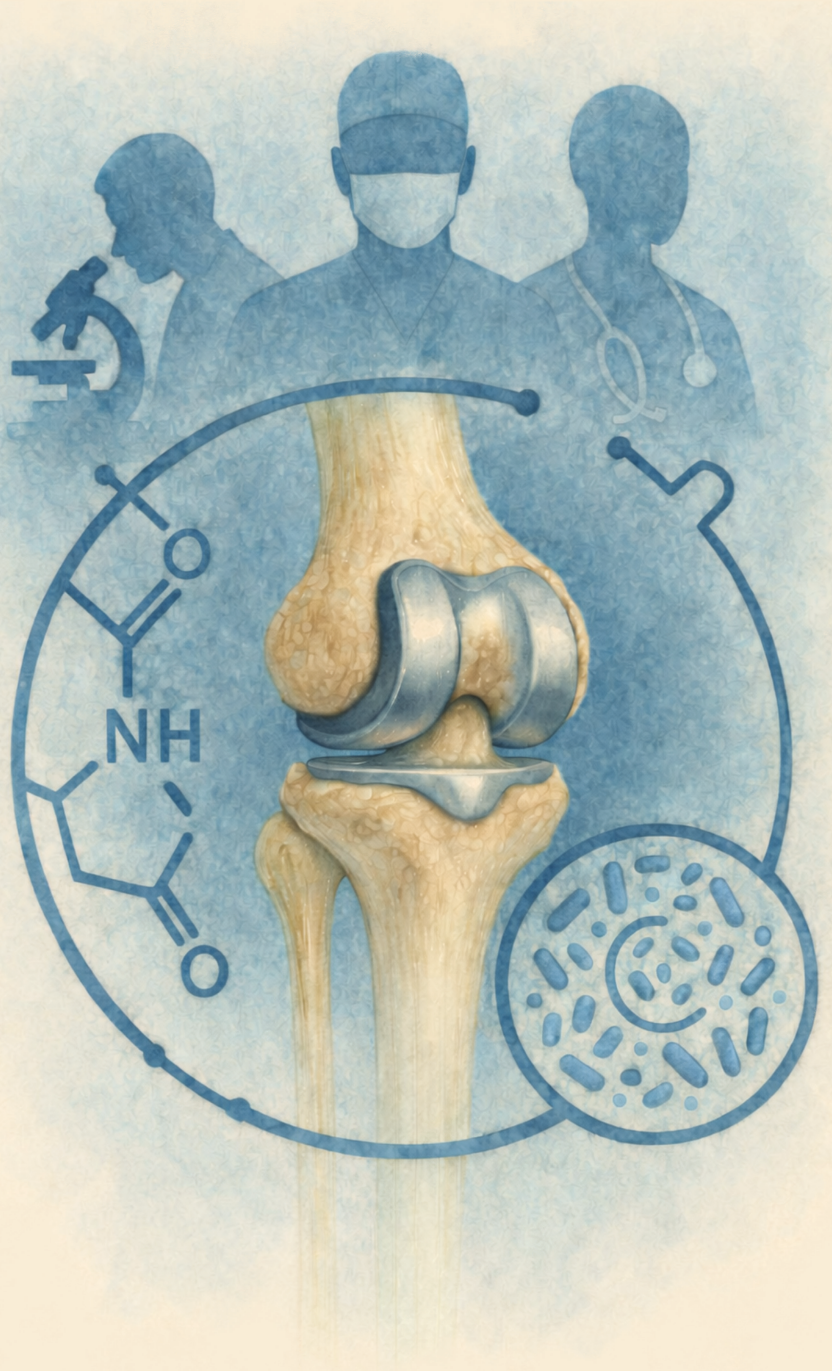
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Part III

Suppressive antimicrobial therapy for prosthetic joint infections

Chapter 5

Global practice variation of suppressive antimicrobial treatment for prosthetic joint infections: A cross-sectional survey study

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Abstract

Objectives To identify global differences in the use of suppressive antimicrobial therapy (SAT) in the management of prosthetic joint infection (PJI).

Methods An online survey was designed to investigate clinician's approach to SAT for PJI, including indications, preferred antimicrobial drugs, dosing, treatment duration and follow-up. The survey was distributed to members of four international (bone and joint) infection societies and study groups.

Results Respondents comprised 330 physicians (204 infectious diseases specialists, 110 orthopedic surgeons, 23 clinical microbiologists) from 43 different countries (Europe, n=134, 41%; Oceania n=112, 34%; North America, n=51, 16%; other, n=33, 10%; total response rate 20%). After debridement, antibiotics and implant retention (DAIR) or one-stage revision, SAT would be initiated often or almost always by 38% of respondents from North America, but only in 6% from Europe and 7% from Oceania. First choices of SAT for staphylococcal PJI were oral cephalosporins (39%) and tetracyclines (31%) in North America; tetracyclines (27%) and anti-staphylococcal penicillins (22%) in Europe; and anti-staphylococcal penicillins (55%) in Oceania. There was no global or regional preferred SAT regimen for Gram-negative PJI. Of all respondents, dosage of SAT was never lowered (n=126, 38%), lowered for specific antibiotics (n=125, 38%) or lowered for all antibiotics (n=79, 24%). SAT was prescribed for a lifelong duration (n=43, 13%), a fixed duration (range 6 months–3 years) (n=104, 32%) or for an undetermined duration (n=154, 47%).

Conclusions Approach to SAT in PJI is highly regional, with no consensus regarding the indication, selection, dose, or duration of SAT between physicians worldwide. This reflects the paucity of data and need for high quality studies to define the optimal use of SAT in the treatment of patients with PJI.

Introduction

Prosthetic joint infection (PJI) is a grievous complication of arthroplasty requiring antibiotics and surgical debridement with- or without or exchange arthroplasty. Following the initial antimicrobial treatment regimen, patients often receive extended antimicrobial therapy, commonly referred to as suppressive antibiotic therapy (SAT). SAT may be started after surgical debridement when risk factors that are associated with a high relapse rate of infection are present, or when surgery is not possible or refused by patients (1). The precise indications for SAT in patients with a PJI are not clear, because the available data on SAT are scarce and of low quality (1-3). The Infectious Diseases Society of America's (IDSA) 2013 guideline on PJI contains recommendations for SAT regimens and dosing, mostly based on expert opinion (4). Moreover, there is no uniform definition of SAT and the optimal treatment duration is unknown (1). The considerable global variation in the use of SAT for PJI belies this lack of data (5-13).

This study aimed to identify international differences for the most common indications and antimicrobial treatment strategies for SAT and to determine discrepancies to guide the direction of further research. For this purpose, we developed a survey on the clinical practice of SAT in PJI, which was distributed across the globe to medical specialists with a special interest in PJI.

Methods

Study and survey design

This was an international cross sectional survey study. A first draft of the survey was constructed by a team of infectious diseases (ID) specialists, clinical microbiologists, orthopaedic surgeons, and clinical epidemiologists specialized in PJI (JLJH, HMJvdL, RJPvdW, JvP, MGJG, MGJdB, HS). From clinical experience and literature review, the team identified unsettled aspects of SAT to be included in the survey. This draft was discussed and amended by the team, leading to a second version, which was reviewed by an international panel of experts (MWB, JSD, DD, LM, DC, AOM, NWCP, AS). This resulted in the final survey consisting of 21 questions on the following topics: organization of care, indication and risk factors; treatment phase before SAT; preferred antimicrobial drug; dosing and treatment duration; follow-up of patients. Respondents were asked to use the definitions of acute and chronic PJI they employ in their daily practice. The survey was in English, voluntary and anonymous. Both the survey design and the collection and management of data were performed

using Formdesk web-based software (Innovero Software Solution B.V., Wassenaar, the Netherlands) hosted at Leiden University Medical Center. The complete survey is available as supplementary data (Suppl. 1).

Ethics approval

A declaration of exemption was issued by the institutional review board of Leiden University Medical Center due to the anonymous and voluntary participation of the survey, reference number nWMODIV2_2024005. By filling in the survey, respondents gave consent to use their data.

Survey distribution

The link to the online survey was sent by email to all members of the European Society of Clinical Microbiology and Infectious Diseases Study Group for Implant-Associated Infections (ESGIAI), the European Bone and Joint infection Society (EBJIS), the Musculoskeletal Infection Society (MSIS) and mailing groups of the Australasian Society of Infectious Diseases (ASID). In addition, all recipients were encouraged to share the survey with colleagues in their network who were involved in PJI care but were member of the above mentioned groups. Recipients were emphatically asked to only fill out the survey if they were actively involved in the treatment of PJI. We estimated that a minimum of 250 respondents would provide reliable results and would be feasible considering the specificity of the topic. The survey was distributed on 12th of March 2024, followed by two reminders by email, and collection of data concluded 12th of April 2024. No financial incentives were offered to the respondents.

Statistical analysis

Returned surveys with less than three questions answered were excluded. Data were summarized using descriptive statistics. Data for categorical variables were presented as proportions or percentages of the number of respondents and stratified per region when feasible and clinically relevant. The estimated response rate was calculated by dividing the reported number of memberships of the respondents by the total number of sent invitation mails to the members of the aforementioned societies. It was assumed that non-member respondents had a similar response rate as members, hence the estimated overall response rate was extrapolated from the member response rate. SPSS Statistics (Version 29.0.0.0, IBM Corporation, Armonk, New York, USA) was used to perform all calculations.

Results

The survey was distributed to all 1483 members of the listed societies and groups. From 42 different countries on 6 six different continents, 330 respondents (223 members of one society, 34 members of two societies, 73 non-members) completed the survey, resulting in an estimated response rate of 20%. A list of the number of respondents per country is provided in Supplementary Table 1. Most respondents (n=291, 88%) completed the full survey. The remaining 39 respondents answered at least 18 of 21 questions (86%). The experience and professional background of the respondents are summarized in Table 1.

Table 1. baseline characteristics of respondents (n=330)

Continent	N (%)
Europe	134 (41)
Oceania	112 (34)
North America	51 (16)
Other[a]	33 (10)
Medical specialty[b]	
Infectious Diseases[c]	204 (63)
Orthopaedic Surgery	110 (33)
Clinical Microbiology	23 (7)
Orthopaedic surgeons per continent	
Europe	50 (37)
Oceania	23 (21)
North America	19 (37)
Other[a]	18 (55)
Years registered as consultant	
in training	9 (3)
<5 years	56 (17)
5-10 years	79 (24)
11-15 years	68 (21)
>15 years	118 (36)
Number of patients with PJI on SAT involved in per year	
1-5	66 (20)
6-10	72 (22)
11-15	50 (15)
>15	141 (43)

Table 1. baseline characteristics of respondents (n=330) *(Continued)*

Member of society[d]	
EBJIS	96 (29)
ASID	96 (29)
MSIS	52 (16)
ESGIAI	47 (14)
non-member	73 (22)
Estimated response rate per society	
EBJIS	19%
ASID	19%
MSIS	21%
ESGIAI	22%

[a]South America, Asia and Africa combined

[b]7 respondents were registered as both ID specialist and microbiologist

[c]9 respondents were internal medicine specialists that for the purpose of this survey were counted as ID specialist

[d]34 respondents were member of two societies

Organization of care

Standard practices regarding consultation, diagnostic strategies and follow-up of patients with SAT are summarized in Table 2. Respondents from Europe (n=90, 67%) were more frequently part of a multidisciplinary team (MDT) for PJI than respondents from other continents (range 24-38%). According 140 respondents (42%), surgeons did not follow-up patients on SAT. In Europe, outpatient clinic follow-up was more commonly conducted solely by surgeons (n=36, 27%) compared to Oceania (n=2, 2%) and North America (n=2, 4%).

Table 2. Organization of care for patients with PJI on SAT

	Total (n=330)	Europe (n=134)	Oceania (n=112)	North America (n=51)	Other continents[a] (n=33)
Consultation other specialty on SAT					
Multidisciplinary team	153 (46)	90 (67)	42 (38)	12 (24)	9 (27)
Other than multidisciplinary team	119 (36)	28 (21)	44 (39)	32 (63)	15 (46)
No	58 (18)	16 (12)	26 (23)	7 (14)	9 (27)
Parameters used for the decision to start SAT					
Inflammatory parameters	220 (67)	85 (63)	79 71)	32 (63)	24 (73)
Imaging	68 (21)	34 (25)	19 (17)	7 (14)	8 (24)
Clinical performance	284 (86)	112 (84)	103 (92)	44 (86)	25 (76)
Follow-up of patients					
Follow-up performed by					
Surgeon and ID specialist and/or GP	144 (44)	50 (38)	54 (48)	28 (55)	11 (33)
Surgeon only	46 (14)	36 (27)	2 (2)	2 (4)	6 (18)
ID specialist only (or together with GP)	133 (41)	44 (33)	53 (48)	20 (39)	16 (49)
GP only	4 (2)	2 (2)	2 (2)	0	0
Frequency of follow-up after 1st year on SAT					
2-4 times a year	232 (70)	92 (69)	75 (67)	36 (71)	29 (88)
Yearly	46 (14)	16 (12)	18 (16)	11 (22)	1 (3)
Once every two years	3 (1)	2 (2)	0	1 (2)	0
Only on patient request	27 (8)	10 (8)	15 (13)	0	2 (6)
Don't know/other	22 (7)	14 (10)	4 (4)	3 (6)	1 (3)

Table 2. Organization of care for patients with PJI on SAT *(Continued)*

	Total (n=330)	Europe (n=134)	Oceania (n=112)	North America (n=51)	Other continents[a] (n=33)
Standard investigations					
Inflammatory parameters	283 (86)	116 (87)	97 (87)	41 (80)	29 (88)
Complete blood count	225 (68)	86 (64)	83 (74)	35 (69)	21 (64)
Kidney function	240 (72)	92 (69)	84 (75)	36 (71)	28 (85)
Liver enzymes	222 (67)	85 (63)	81 (72)	34 (67)	22 (67)
Imaging	89 (27)	43 (32)	22 (36)	12 (24)	12 (36)

[a]South America, Asia and Africa combined

GP: general practitioner

Clinical scenarios and risk factors determining the choice for SAT

Box 1. For the following scenarios, how often would you place the patient on SAT? rarely (=0-25%), sometimes (=26-50%), often (=51-75%), almost always (=76-100%)

1. Acute PJI successfully treated with DAIR without additional risk factors[a] for failure
2. Acute PJI successfully treated with DAIR + ≥ 1 risk factors[a] for failure
3. Chronic PJI treated with DAIR
4. PJI successfully treated with one stage revision
5. PJI with failure of DAIR#
6. PJI with failure of one stage revision[b]
7. PJI treated with antibiotic therapy only (no surgery) but with a draining fistula
8. PJI treated with antibiotic therapy only but no draining fistula present

[a]Those included in figure 2 (e.g. no change of modular component, chemotherapy, megaprosthesis, difficult to treat micro-organisms, etc)
[b]preference for debridement followed by SAT over other surgical options

To investigate the indications for SAT, respondents were asked how often they would place a patient on SAT in eight different clinical scenarios (Box 1). The results from Europe, Oceania and North America are summarized in Figure 1 and supplementary Figure 1. The number of respondents from South America, Asia and Africa were too small to include in this analysis. Most striking was that in patients with acute PJI treated with DAIR or one-stage revision (1SR), nineteen North American (38%) would often or nearly always give SAT as compared to eight European (6%), and seven Oceanian respondents (7%) (figure 1A and supplementary figure 1A). In scenarios 2, 3, 5, 6 and 7, respondents from North America also initiated SAT more frequently compared to European respondents, but a considerable heterogeneity existed within continents for these scenarios (Figure 1B-D and supplementary Figure 1B-C). For patients with PJI who are not treated with surgery, most respondents from Europe, Oceania and North America answered that SAT is indicated, providing patients did not have fistula (SAT initiated 'almost always' or 'often' by 82% of all respondents) (Supplementary Figure 1D).

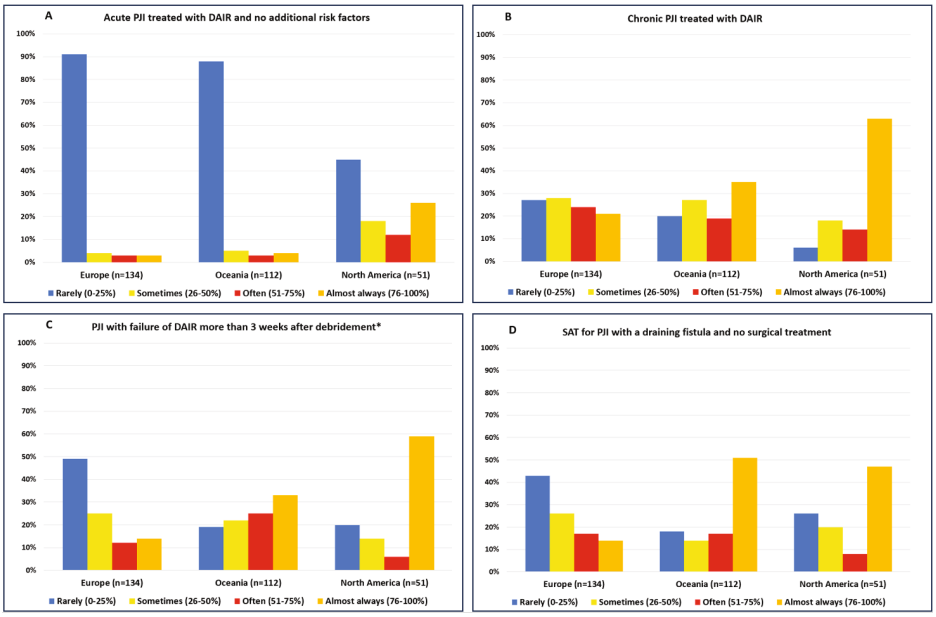

Figure 1. *Clinical scenarios of patient with PJI of which respondents were asked how often they would place patient on SAT stratified per continent. *preference for debridement followed by SAT instead of other surgical options*

The host risk factors for failure considered as an indication for initiating SAT in acute PJI treated with DAIR are summarized in Figure 2. The top five microbiological factors that were reported as indication for SAT were infection with Candida species (n=128, 39%), Pseudomonas species (n=71, 22%), rifampicin-resistant staphylococci (n=70, 21%), methicillin-resistant Staphylococcus aureus (MRSA) (n=61, 18%), and enterococci (n=51, 15%). For 148 respondents (45%), the causative microorganism did not influence the decision to initiate SAT providing an adequate DAIR was performed.

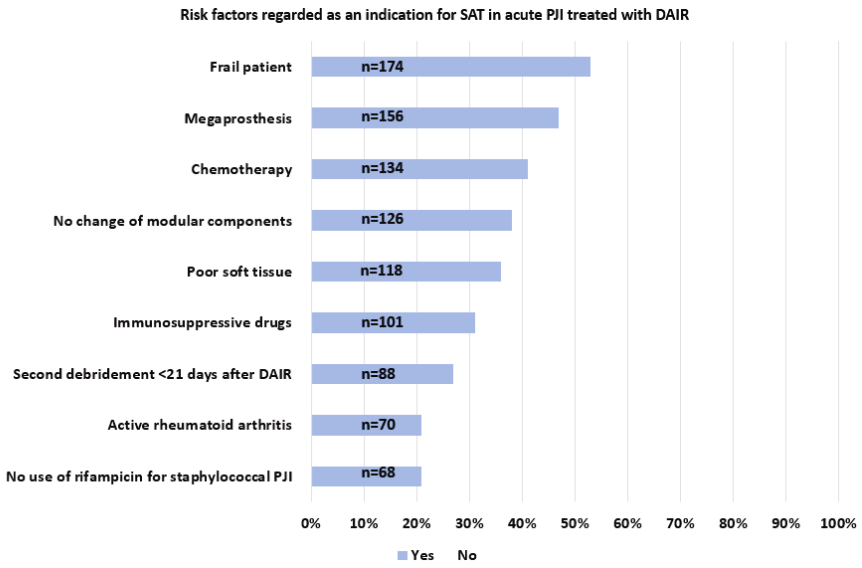

***Figure 2**. Risk factors regarded by >20% of all respondents (n=330) as an indication for SAT in acute PJI treated with DAIR*

Antimicrobial strategy: choice, dose and treatment duration of SAT

Preferred SAT regimens for staphylococcal PJI differed significantly between continents (Figure 3a). Anti-staphylococcal penicillins are rarely used in North America (n=3, 6%) but are preferred in Oceania (n=61, 55%). For streptococcal PJI, most respondents from Europe, Oceania and North America would prescribe a penicillin (Figure 3b). The preferred SAT-regimen for Gram-negative PJI was heterogeneous within and between these three continents (Figure 3c). A detailed overview of all first and second choice SAT regimens, stratified per continent, are provided in supplementary Table 2-4.

With respect to the dosing of SAT, 79 respondents (24%) routinely switch to a lower than therapeutic oral dosage when initiating SAT for PJI, 125 respondents (38%) would consider a lower dose for selected antimicrobials and/or in case of side-effects and 126 respondents (38%) would never lower the dose (Supplementary Table 5). The majority of respondents (n=176, 53%) reported not having a predefined treatment duration, whereas 111 respondents (34%) indicated they stop SAT after 6 months to 3 years in the setting of a good clinical course and normalized inflammatory parameters; only a small proportion (n=43, 13%) indicated they never stop SAT, regardless of the clinical course.

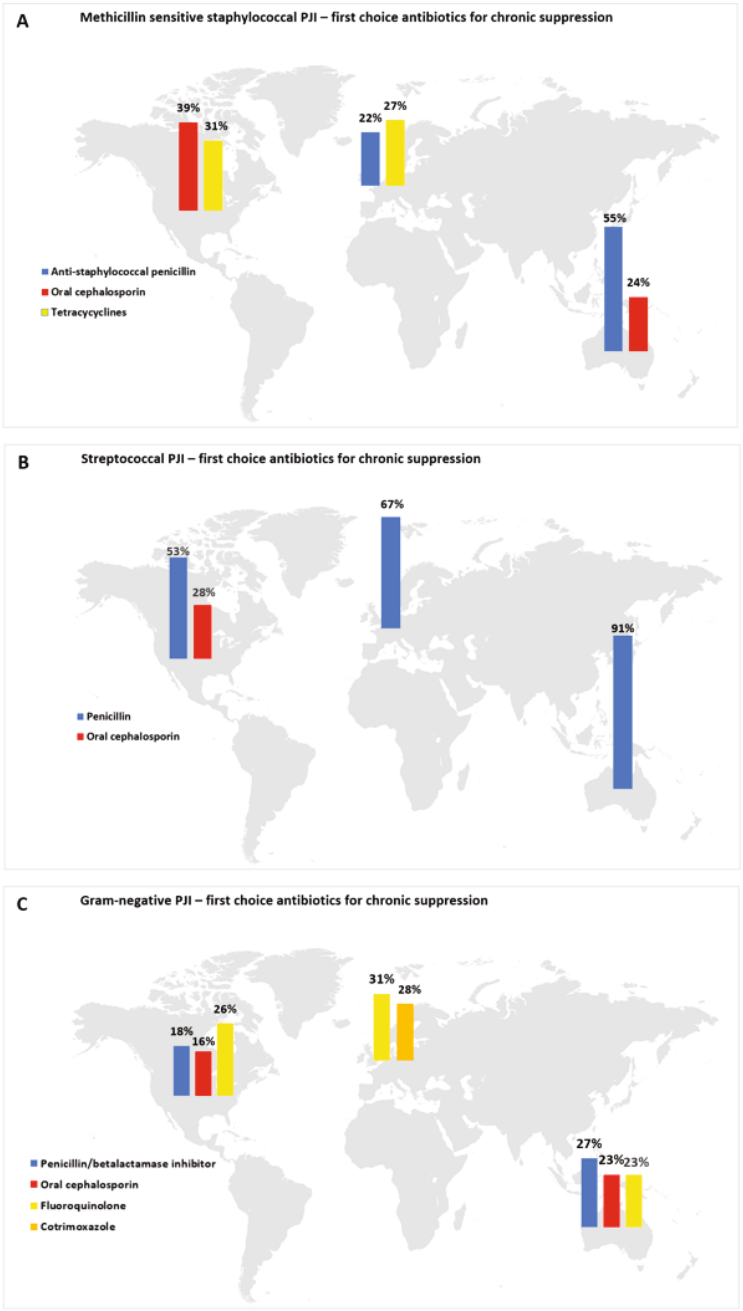

Figure 3. *Antibiotic treatment preferred for suppressive therapy per continent. Percentage of total respondents of the question per continent. Europe: n=134; Oceania: n=112; North America: n=51.*

Discussion

This survey study revealed substantial global variation in the use of SAT in the management of patients with PJI. Variations existed in all aspects of SAT: indications, antimicrobial strategy, dosage and duration of antibiotic treatment and the organization of care.

Organization of care

Respondents from Europe participated more often in an MDT than the rest of the world. Multiple studies reported improved outcomes after installing MDTs and implementation of MDTs for PJI is recommended by several orthopaedic societies and experts (14-16). Possible barriers to the establishment of MDTs are a lack of time, financial support and/or inappropriate infrastructure (17). Nearly all orthopaedic surgeons consulted ID physicians or microbiologists about the antimicrobial treatment even in the absence of a MDT. Remarkably, according to 42% of respondents, the surgeon was not involved in outpatient follow-up.

Indication for SAT

Respondents from North America were more inclined to treat patient with SAT than European respondents. For patients with acute PJI treated with DAIR or 1SR, 38% of North American respondents would likely initiate SAT while this was rarely the case in Europe and Oceania. This difference in management was also demonstrated in a recent retrospective study on SAT following DAIR for acute PJI; In the US 160/184 patients (87%) received SAT and in Europe 7/226 patients (3%) (18). These contrasting approaches are probably based on dissimilarities between American and European guidelines. Interestingly, in the IDSA 2013 guideline committee, only one out of three European panel members would consider SAT in patients after DAIR and rifampicin-based therapy for staphylococcal PJI or fluoroquinolones for Gram-negative PJI, while all six American members considered SAT for all patients after DAIR (4). A recent survey study from the United States (n=413) showed that the majority of ID specialists would initiate SAT for patients after DAIR or 1SR (19). On the other hand, several national guidelines on PJI in Europe do not recommend suppression after DAIR for acute PJI or after 1SR (20, 21). These differences in guideline recommendations probably explain the more frequent use of SAT in the United States compared to Europe.

Overall, large heterogeneity was observed regarding the perceived indications for SAT; in particular in patients with chronic PJI treated with DAIR, patients with failure after DAIR or 1SR and patients with a draining fistula. In a retrospective multicenter

study including patient with PJI and a fistula, most patients received SAT (63/72, 88%) although this did not prevent long-term complications (22). A recent review identified recurrent PJI, severe immunosuppression, *Staphylococcus aureus,* and no exchange of polyethylene liner as factors for which SAT is likely beneficial after DAIR (23). Remarkably, the majority of respondents in our survey, did not regard these risk factors an indication for suppression in acute PJI treated with DAIR. The most important risk factors according to the respondents were frailty and presence of a megaprosthesis. Rifampicin-resistant staphylococci were considered an indication for SAT in acute PJI treated with implant retention by only 21% of respondents, which is in contrast with the IDSA guideline and several studies (4, 7, 23).

Antimicrobial regimens

Substantial diversity was observed between and within Europe, Oceania and North America in the preferred antimicrobials for SAT except for streptococcal PJI. The near absence of the use of oral cephalosporins in Europe is probably due to differences in antimicrobial stewardship and policies. The infrequent use of anti-staphylococcal penicillins by North American respondents could reflect the high MRSA prevalence in community-acquired staphylococcal infections in the US, which is why pharmacies do not stock up on these drugs anymore. Currently, the IDSA 2013 guideline is the only guideline recommending specific antimicrobial regimens, but adherence to those recommendations by respondents was low, likely due to the low quality of available clinical data (4). The effectiveness of tetracyclines, beta-lactams, fluoroquinolones and cotrimoxazole was comparable in the three largest studies on SAT in PJI (combined n=572) with success rates between 59% and 65% (6, 8, 13). To investigate the optimal antibiotics for suppression, large multicenter randomized trials are needed.

Dosage, duration and definition of SAT

One third of respondents would never lower the standard therapeutic dosage for PJI in case of SAT while the majority would do this either routinely or in specific situations. The IDSA recommendations for lower dosages for some antimicrobials are based on expert opinion; studies focusing on the dosing of SAT are scarce (4). Although it is common practice for most physicians world-wide to use a relatively low dosage of antibiotics for SAT, to date there is only one observational study on this approach which reported no difference in failure-free survival between patients with an orthopaedic implant infection treated with low-dosage compared to normal-dosage SAT (24). More data are necessary to inform on the effectivity and risk of antimicrobial resistance development of low dosed SAT.

Most studies mention that chronic SAT is prescribed indefinitely (4, 6-8, 10, 11). In contrast, the vast majority of respondents (>85%) stops or at least considers stopping SAT after a certain amount of time. This observation suggests that most respondents assume that cure can be achieved after a certain duration of SAT. Most relapses in these patients occur in the first two years and limited data suggest similar patient outcomes whether or not SAT is continued beyond this point (6-8, 11, 13, 24).

Definition of SAT

In most European publications, SAT is defined as lifelong antibiotic treatment of 'incurable infections' (patients treated with suboptimal or no surgery) (6-8, 10, 11). Studies from the United States mainly reserve the term SAT for an extended treatment duration after DAIR (13, 25-27). These two 'concepts' of SAT represent two distinct treatment strategies with a different goal and duration aimed at patient categories with variable prognoses. To improve the interpretation of future research, we propose to make a differentiation between these categories by using the following definitions: *Fixed term SAT*: prolonged antimicrobial therapy for a fixed duration of 6-24 months with the main goal of curing the infection.

Indefinite SAT: antimicrobial therapy with an undetermined duration with the main goal to prevent a relapse. In both definitions, SAT is started after the infection is clinically controlled following the standard treatment as established by (inter)national or local guidelines.

Strengths and limitations

To our knowledge, this is the first global survey on SAT for PJI, which revealed a great variation of SAT practices and identified relevant knowledge gaps that need to be prioritized and addressed in clinical research on treatment of PJI. Limitations of the study are the small number of respondents from North America, Asia, South Africa and South America, reducing its generalizability. Furthermore, difference in baseline characteristics between non-responders and responders are unknown, possibly introducing bias. Lastly, it is likely that respondents vary in SAT dose and treatment duration according to the indication for SAT, but we did not survey this specifically. Furthermore, comparing answers between respondents should be done with the notion that we did not ask respondents for their definition of SAT. The response rate was relatively low, but we expected this beforehand because of the specificity of the subject and the request to recipients to only fill out the survey if they were knowledgeable about PJI and had sufficient clinical experience treating patients with SAT.

Summary and conclusions

The global clinical practice of using SAT for patients with PJI is highly heterogeneous and based on expert opinion and observational studies, leaving many clinical questions unanswered. To optimize and harmonize treatment for these patients, future research and guidelines should focus on the indication for SAT and optimal antimicrobial regimens including dosage and duration. A uniform definition of SAT is needed to better compare the outcomes of studies and further improve their clinical value.

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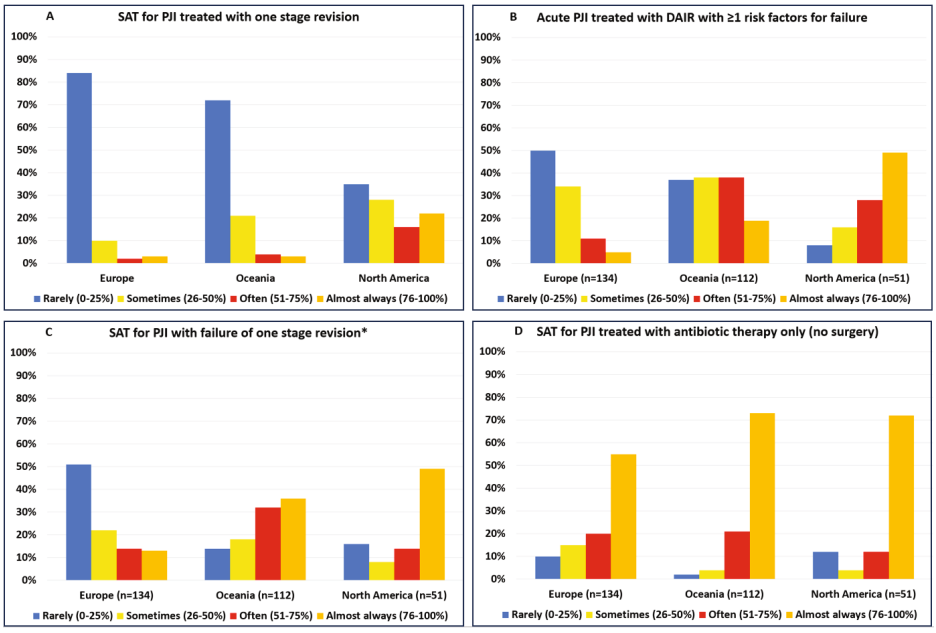
Supplement



Supplementary Figure 1. *Clinical scenarios of patients with PJI of which respondents were asked how often they would place patient on SAT stratified per continent. *preference for debridement followed by SAT instead of other surgical options.*

Supplementary Table 1. Number of respondents per country

Argentina	1
Australia	92
Austria	3
Belgium	3
Bosnia and Herzegovina	1
Brazil	3
Canada	5
China	1
Colombia	1
Croatia	2
Czech Republic	1
Denmark	1
Egypt	1
Finland	2

Supplementary Table 1. Number of respondents per country *(Continued)*

France	5
Germany	6
Greece	5
Hungary	1
India	7
Iran	1
Ireland	3
Italy	8
Korea, republic of	2
Lithuania	3
Netherlands	25
New Zealand	20
Nicaragua	2
Norway	3
Philippines	2
Portugal	7
Romania	1
Singapore	2
Slovenia	1
South Africa	2
Spain	28
Sweden	3
Switzerland	6
Thailand	3
Tunisia	2
Turkey	2
United Kingdom	16
United States	46

Supplementary Table 2. First and second choice SAT for staphylococcal PJI

First choice antibiotic	All respondents	Europe	Oceania	North America	Other continents[a]
	n=330	n=134	n=112	n=51	n=33
Anti staphylococcal penicillins	100 (30)	30 (22)	61 (55)	3 (6)	6 (18)
Oral cephalosporins	61 (18)	6 (5)	27 (24)	21 (41)	7 (21)
Tetracyclines	58 (18)	36 (27)	5 (5)	16 (31)	1 (3)
Cotrimoxazole	26 (8)	17 (13)	4 (4)	2 (4)	3 (9)
Rifampicin/fluoroquinolone	25 (8)	11 (8)	3 (3)	3 (6)	8 (24)
Rifampicin/non-fluoroquinolone	18 (6)	8 (6)	6 (5)	2 (4)	2 (6)
Fluoroquinolone	12 (4)	9 (7)	0	0	3 (9)
Clindamycin	9 (3)	6 (5)	1 (1)	0	2 (6)
Linezolid	0	0	0	0	1 (3)
No preference/per order ID specialist or microbiologist	20 (6)	11 (8)	5 (5)	4 (8)	0
Second choice antibiotic					
Anti staphylococcal penicillins	36 (11)	9 (7)	22 (20)	2 (4)	3 (9)
Oral cephalosporins	73 (22)	7 (5)	48 (43)	15 (29)	3 (9)
Tetracyclines	58 (18)	24 (18)	9 (8)	21 (41)	4 (12)
Cotrimoxazole	51 (16)	30 (22)	10 (9)	3 (6)	8 (24)
Rifampicin/fluoroquinolone	11 (3)	6 (5)	2 (2)	1 (2)	2 (6)
Rifampicin/ non-fluoroquinolone	16 (5)	8 (6)	5 (5)	1 (2)	2 (6)
Fluoroquinolone	6 (2)	3 (2)	1 (1)	1 (2)	1 (3)
Clindamycin	43 (13)	29 (22)	9 (8)	1 (2)	4 (12)
Linezolid	7 (2)	3 (2)	0	0	4 (12)
No preference/per order ID specialist or microbiologist	29 (9)	15 (11)	6 (5)	6 (12)	2 (6)

[a]South America, Asia and Africa combined

Supplementary Table 3. First and second choice SAT for streptococcal PJI

First choice antibiotic	All respondents	Europe	Oceania	North America	Other continents[a]
	n=330	n=134	n=112	n=51	n=33
Penicillins	234 (71)	90 (67)	102 (91)	27 (53)	15 (45)
Oral cephalosporins	30 (9)	7 (5)	4 (4)	14 (28)	5 (15)
Tetracyclines	5 (2)	4 (3)	0	1 (2)	0
Cotrimoxazole	7 (2)	6 (5)	0	0	1 (3)
Rifampicin/fluoroquinolone	9 (3)	4 (3)	0	1 (2)	4 (12)
Rifampicin/non-fluoroquinolone	3 (1)	1 (1)	1 (1)	1 (2)	0
Fluoroquinolone	10 (3)	5 (4)	0	2 (4)	3 (9)
Clindamycin	8 (2)	3 (2)	0	0	5 (15)
No preference/per order ID specialist or microbiologist	24 (7)	14 (11)	5 (5)	5 (10)	0
Second choice antibiotic					
Anti staphylococcal penicillins	32 (10)	10 (8)	2 (2)	13 (26)	7 (21)
Oral cephalosporins	121 (37)	17 (13)	76 (68)	21 (41)	7 (21)
Tetracyclines	25 (8)	15 (11)	2 (2)	6 (12)	2 (6)
Cotrimoxazole	14 (4)	9 (7)	3 (3)	0	2 (6)
Rifampicin/fluoroquinolone	5 (2)	1 (1)	2 (2)	0	2 (6)
Rifampicin/non-fluoroquinolone	5 (2)	3 (2)	1 (1)	1 (2)	0
Fluoroquinolone	13 (4)	6 (5)	3 (3)	0	4 (12)
Clindamycin	62 (19)	48 (36)	10 (9)	1 (2)	3 (9)
Linezolid	4 (1)	1 (1)	0	0	3 (9)
No preference/per order ID specialist or microbiologist	49 (15)	24 (18)	13 (12)	9 (18)	3 (9)

[a]South America, Asia and Africa combined

Supplementary Table 4. First and second choice SAT for gram-negative PJI

First choice antibiotic	All respondents	Europe	Oceania	North America	Other continents[a]
	n=330	n=134	n=112	n=51	n=33
Fluoroquinolone	102 (31)	42 (31)	26 (23)	13 (26)	21 (64)
Cotrimoxazole	67 (20)	38 (28)	18 (16)	6 (12)	5 (15)
Penicillin/beta-lactamase	63 (19)	19 (14)	30 (27)	9 (18)	5 (15)
inhibitor Oral cephalosporins	40 (12)	4 (3)	26 (23)	8 (16)	2 (6)
Tetracyclines	14 (4)	6 (5)	0	8 (16)	0
Fosfomycin	2 (1)	2 (2)	0	0	0
No preference/per order ID specialist or microbiologist	42 (13)	23 (17)	12 (11)	7 (14)	0
Second choice antibiotic					
Fluoroquinolone	62 (19)	30 (22)	18 (16)	9 (18)	5 (15)
Cotrimoxazole	107 (32)	46 (34)	35 (31)	17 (33)	9 (27)
Penicillin/beta-lactamase inhibitor Oral cephalosporins	44 (13)	11 (8)	23 (21)	5 (10)	5 (15)
	36 (11)	9 (7)	18 (16)	4 (8)	5 (15)
Tetracyclines	15 (5)	8 (6)	2 (2)	4 (8)	1 (3)
Fosfomycin	4 (2)	1 (1)	0	0	3 (9)
No preference/per order ID specialist or microbiologist	62 (19)	29 (22)	16 (14)	12 (24)	5 (15)

[a]South America, Asia and Africa combined

Supplementary Table 5. Dosing of SAT

Respondents that lower the dosage of this antimicrobial, n (%)	Total	Europe	Oceania	North America	Other continents[a]
	n=330	n=132	n=112	n=51	n=33
Penicillins	142 (43)	60 (45)	60 (54)	18 (35)	4 (12)
Oral cephalosporins	126 (38)	44 (33)	62 (55)	18 (35)	2 (6)
Tetracyclines	91 (28)	47 (36)	32 (29)	9 (18)	3 (9)
Fluoroquinolones	102 (31)	48 (36)	36 (32)	14 (27)	4 (12)
Cotrimoxazole	124 (38)	58 (44)	42 (38)	17 (33)	7 (21)
Clindamycin	99 (30)	48 (36)	36 (32)	10 (20)	5 (15)
Respondents lowering the dosage of SAT, n (%)					
Never	126 (38)	47 (36)	35 (31)	22 (43)	22 (67)
Always	79 (24)	39 (30)	29 (26)	9 (18)	2 (6)
In selected antibiotics	125 (38)	48 (36)	48 (43)	20 (39)	9 (27)

[a]South America, Asia and Africa combined

Chapter 6

Practice variation, outcomes and definitions of suppressive antimicrobial therapy for prosthetic joint infections: a systematic review and expert consensus statement

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Abstract

Background Literature on periprosthetic joint infection (PJI) contains varying strategies and definitions of suppressive antimicrobial therapy (SAT). This study aimed to describe current SAT strategies, evaluate their clinical outcomes, and establish a consensus definition of SAT for research and clinical purposes.

Methods Following PRISMA guidelines, a systematic review was performed by searching PubMed and EMBASE from their inception to March 10, 2025. All trials and observational studies including ≥10 patients with PJI treated with SAT were eligible. Data on study, patient, and treatment characteristics, definitions and outcomes were extracted. Study quality was appraised using the Methodological Index for Non-randomized Studies tool. A random effects model was used to pool success rates. Definitions were developed through a modified Delphi process.

Results Forty-two studies (n = 2524 patients) were included: 25 from the United States (U.S.) and 17 from Europe. In U.S. literature, SAT was predominantly prescribed for acute PJI managed with debridement, antibiotics, and implant retention (DAIR), whereas European studies primarily involved PJI managed without curative intent. The pooled reported success rate of SAT was 74% (95% CI: 63-85%) for acute PJI treated with DAIR and 70% (95% CI: 63-78%) for chronic PJI treated with DAIR or without surgery. Definitions of SAT were inconsistently reported. Consensus was achieved, resulting in definitions distinguishing SAT from extended antimicrobial therapy (EAT).

Conclusion SAT is inconsistently defined in PJI literature with variation of practice between the U.S. and Europe. To harmonize research and clinical communication, we advocate the use of consensus definitions of SAT and EAT.

Introduction

Periprosthetic joint infection (PJI) is a serious complication of arthroplasty necessitating antibiotics and surgical debridement with or without exchange arthroplasty to achieve cure. After completion of the initial therapeutic antimicrobial regimen, physicians often continue antimicrobial treatment, commonly referred to as suppressive antimicrobial therapy (SAT). The indications for this treatment strategy vary worldwide and no uniform definition of SAT currently exists (1). For example, the Infectious Diseases Association of America (IDSA) in their 2012 guideline recommends indefinite SAT for PJI treated with Debridement, Antibiotics and Implant Retention (DAIR), implying this is a non-curative strategy (2). From a European perspective, however, DAIR is generally regarded as a curative procedure for acute PJI and is therefore not standardly followed by suppressive therapy. In Europe, the term SAT is used only for long-term antimicrobial strategies in situations considered non-curative—such as in patients who would normally have an indication for exchange arthroplasty but are nonetheless treated with DAIR, or in those managed without surgical debridement (3-5). To our knowledge, national guidelines specifically addressing PJI management are not available outside Europe and the United States (U.S.). These differences in clinical practice are reflected in the heterogeneous methodology of studies evaluating SAT. Across studies, SAT is variably defined and considered as a treatment strategy or as a marker for treatment failure. This inconsistency introduces misclassification bias and limits comparability of data on PJI treated with SAT. We therefore performed a systematic review to (1) characterize current SAT practices, (2) summarize and compare reported clinical outcomes, and (3) ultimately propose a consensus based definition of SAT through a modified Delphi process for future research and patient management.

Methods

Search strategy and selection criteria

This systematic review was conducted and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement and registered in the PROSPERO database (registration number CRD420251011557). The population of interest consisted of patients with PJI treated with SAT. Clinical trials, observational studies and case series containing more than ten PJI treated with SAT were eligible for selection. Studies that also included other antimicrobial strategies, or other infections (i.e., other implant-associated infections, osteomyelitis, or septic arthritis) were only included if the variables of interest were reported separately for

PJI. Studies that included fewer than 10 patients with PJI treated with SAT, or that considered SAT as a failure of treatment, were excluded.

The literature search was designed in collaboration with a medical librarian from the Leiden University Medical Center. PubMed and EMBASE databases were searched from inception to March 10, 2025. The complete search terms and strategy are provided in supplementary table 1.

Study selection and data extraction

Literature screening and data extraction were performed with the use of Covidence systematic review software (Veritas Health Innovation Ltd, Melbourne, Australia. Available at www.covidence.org). Two reviewers independently screened titles, abstracts, and full texts of potentially relevant studies to assess eligibility. Data extraction was performed by one reviewer (JLJH). A random 25% sample of included studies was verified by a second reviewer (HS). No discrepancies necessitating third-reviewer adjudication were identified.

Assessment of quality of evidence

The Methodological Index for Non-Randomized Studies (MINORS) assessment tool was used to assess the methodology and quality of the included studies used for quantitative analysis (6).

Data analysis

Data extracted from eligible studies included study characteristics (country or continent, year of publication), patient characteristics (chronicity of infection and the indication for initiating SAT), treatment characteristics (surgical strategy, pre-SAT antimicrobial regimen, SAT dosing, duration, and treatment goals), and outcomes (definition of SAT, definition of failure, reported success rate, and relapse rate after discontinuation). Definitions of acute and chronic infection, as well as failure criteria, were adopted as reported by the original authors; acute infection included both postoperative and hematogenous cases.

The primary quantitative outcome was the reported success rate of SAT in each study. Reported numbers of successful and total treated patients were aggregated across studies at the patient level and within predefined subgroups (based on PJI chronicity, SAT dosing, and treatment duration) to calculate pooled success rates. Due to expected heterogeneity in study populations, treatment protocols, and follow-up durations, a random effects meta-analysis was performed using metafor package in R with Re-

stricted maximum-likelihood estimation (REML) for estimating heterogeneity (I^2) (7). All descriptive statistics were performed using SPSS 23.0 (IBM Corp., Armonk, NY).

Approach for defining SAT

Qualitative data were analyzed by comparing definitions, indications, and treatment strategies across studies and regions to identify recurring concepts and differences. These data were used to inform the expert consensus process described below. The assembled expert panel was based on recognized clinical and academic PJI expertise among investigators who previously collaborated on an international SAT survey that formed the foundation for this consensus effort (1).

Consensus definitions were developed through a modified Delphi process. Preliminary findings from the literature review were summarized and distributed to all co-authors (i.e., panel members) together with a structured questionnaire consisting of 13 questions addressing potential definitional domains and their formulation. All panel members provided feedback, which was collated and used to construct a draft definition accompanied by a summary of comments and rationale for each choice. The draft and accompanying rationale were then redistributed for a second full round of review and feedback. In this round, all panelists re-evaluated each proposed element and provided additional input. A final proposal was then developed with this feedback, and panel members were polled for their approval.

Results

Overview of included studies

The literature search retrieved 2076 articles, of which 91 full-text articles were assessed for eligibility (Figure 1). In total, 42 observational studies, published between 1988 and 2025, comprising 2524 patients, were included (Supplementary file). All studies were from either the U.S. (n=25; 1528 patients) or Europe (n=17; 996 patients). No eligible studies from regions outside the U.S. and Europe were identified through our search strategy. No randomized trials were identified. Forty studies containing 2467 patients reported clinical outcome of included patients and were available for quantitative analysis. According to MINORS assessment, methodological quality was generally low to moderate (Supplementary table 2).

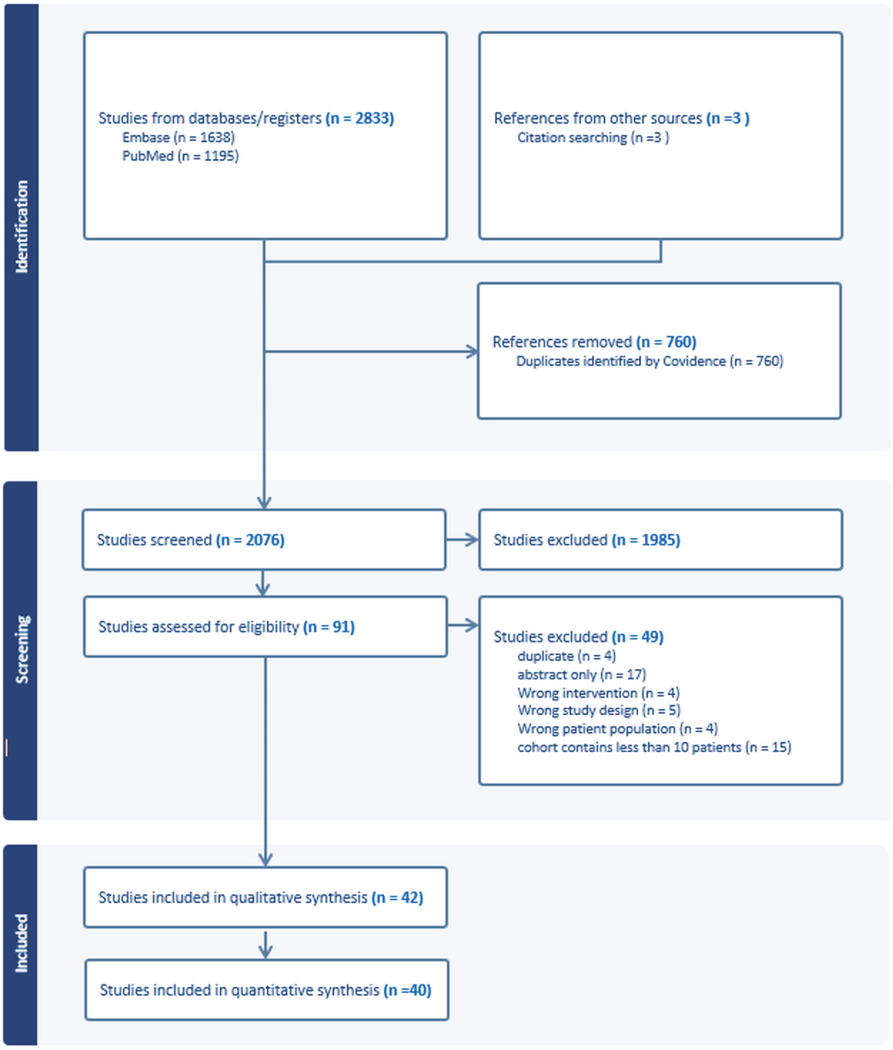

Figure 1. *PRISMA flowchart for the identification, screening, and inclusion of studies. Abbreviations: PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analysis.*

Clinical aspects of SAT

Reported indications for SAT

Of the 25 studies from the U.S., ten reported exclusively on acute PJI managed with DAIR, nearly all published between 2017 and 2024 (Supplementary Refs 1-10). Seven studies included mixed acute and chronic infections (Supplementary Refs 11-17), and five described a reason for SAT beyond implant retention—such as non-surgical man-

agement or DAIR performed in the presence of risk factors like immunosuppression or after failure of a prior DAIR (Supplementary Refs 18-22). Three studies did not report infection chronicity (Supplementary Refs 23-25).

Among the 17 European studies, 15 described SAT as being prescribed in one of two clinical contexts as stated by the authors (Supplementary Refs 26-40). First, to mitigate a high relapse risk following procedures that were not expected to be curative—such as non-surgical management or DAIR performed in the presence of risk factors for failure. Second, in patients who underwent potentially curative surgery (DAIR for acute PJI or exchange arthroplasty) but for whom a relapse was considered unacceptable because of frailty, advanced age, or other comorbidities.

Studies were categorized according to the patient characteristics and indications reported by the authors, reflecting the dominant clinical context within each study (Figure 2).

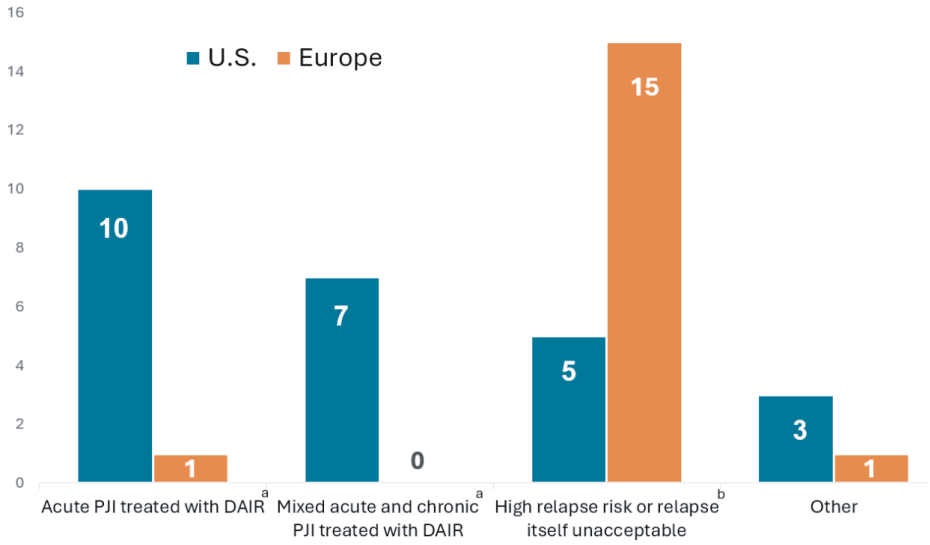

Figure 2. *Reported dominant clinical contexts in which SAT was applied in U.S. and European studies (n = 42)*

Abbreviations: PJI, periprosthetic joint infection; DAIR, debridement, antibiotics and implant retention.

[a]These cohorts included both acute postoperative PJI (within 3–4 weeks after total joint arthroplasty [TJA]) and acute hematogenous PJI (developing > 1 month after TJA but with symptom duration < 3–4 weeks). No reason other than implant retention was provided by the authors.

[b]This high risk was explicitly stated by the authors.

Treatment goals

Treatment goals were variably reported and included: infection control, symptom reduction, prevention of progression, prevention of further surgery, and prosthesis retention. For studies exclusively including acute PJI managed with DAIR, the goal, when specified, was to maximize reoperation-free survival and to prevent recurrence.

Treatment duration

All except one U.S. and one European study reported on treatment duration. Most U.S. studies (n=19) reported that the intended treatment duration was indefinite and the majority of patients were still receiving SAT at final follow-up (average follow-up 51 months, based on reported means or medians). Four studies reported a finite SAT duration (mean 6–18 months), mainly for acute PJI treated with DAIR (Supplementary Refs 1, 3, 4, 8). In one study, patients managed by DAIR who discontinued SAT after a median of six months were compared with those with indefinite therapy (showing no difference in success rate).

In European studies, treatment was intended to be indefinite in 12 and most patients were still on SAT at the end of follow-up (average follow-up 25 months, based on reported means or medians) . Two studies compared patients treated with DAIR who stopped SAT after a defined period (ranging from 6 to 36 months) with those on indefinite therapy; one found no difference in outcome, while one reported a higher success rate in the ongoing SAT group (Supplementary Refs 27, 30). In the only study focusing primarily on acute PJI, SAT was intended for a minimum of 12 months and discontinued in 81% of patients after mean 18 months (Supplementary Ref 41).

Pre-SAT antimicrobial strategy

In U.S. studies, antimicrobial treatment before starting SAT was exclusively intravenous (IV) in 23 studies, and one study initiated SAT orally without any reported pre-treatment.

In European studies, pre-SAT therapy was administered solely IV in eight studies, whereas seven studies reported IV therapy followed by oral antibiotics before transitioning to SAT. The remaining studies in both regions did not specify their pre-SAT regimen.

Dosing

Nine U.S. and ten European studies described SAT dosing. Regimens were interpreted in relation to the 2013 IDSA PJI guideline recommendations for chronic oral antimicrobial suppression (2). Of the nine U.S. studies providing dosing information, five

referenced the IDSA guideline (Supplementary Refs 2, 9, 13, 16, 17, 41). Four used a combination of IDSA-concordant and lower-than-IDSA regimens (Supplementary Refs 11, 15, 21, 22).

Within the ten European studies, exclusively IDSA-concordant regimens were observed in two (Supplementary Refs 30, 36). Both higher-than-IDSA dosing and IDSA-concordant regimens were described in two studies (Supplementary Refs 33, 38), whereas three studies used IDSA-concordant and lower-than-IDSA regimens, with lower dosing predominating (Supplementary Refs 27, 28, 33, 34, 39). One study used tedizolid for suppression, a regimen not included in the IDSA dosing recommendations (Supplementary Ref 38). Two European studies reported the use of therapeutic drug monitoring (TDM); one for dosing IV dalbavancin and the other for subcutaneous beta-lactams (Supplementary Refs 37, 42).

Outcomes of SAT

Forty of 42 included studies reported treatment outcomes. Definitions of treatment success and failure were highly heterogeneous across studies. Most defined failure as reoperation for infection, clinical recurrence or persistence of infection, or infection-related death. Detailed study-specific definitions are provided in Supplementary Table 3.

Pooled analysis of 40 studies (2467 patients) yielded an overall reported success rate of 74% (95% confidence interval (CI) 70%-79%). Acute PJI treated with DAIR had a similar success rate of SAT (74% (95% CI 63%-85%)) compared to chronic PJI (70% (95% CI 63%-78%)). Continent and SAT duration did not alter pooled success rates (Table 1). Patient population, surgical treatment, duration of treatment and follow-up, and success rate for each individual study included in the pooled analysis are summarized in supplementary Table 4. Eight studies on PJI treated with DAIR included a comparator group of patients managed without SAT; their reported outcomes are summarized descriptively in Supplementary Table 5. Five studies reported higher success rates with SAT, whereas three found no significant difference, including the largest cohort (n=510).

Table 1. Pooled data of studies reporting individual patient data regarding suppressive antimicrobial therapy

	N studies	N patients	Pooled success rate N, % [95%CI]
All PJI	40	2467	1806, 74 [70-79]
Indication			
Acute PJI treated with DAIR	11[a]	711	538, 74 [63-85]
Chronic PJI with implant retention	13[a,b]	732	507, 70 [63-78]
Continent			
United States	24	1483	1089, 73 [66-79]
Europe	16	984	717, 77 [70-83]
Duration SAT			
ongoing at final follow-up	25	944	693, 74 [69-80]
discontinued[c]	21	526	410, 74 [64-84]

Abbreviations: PJI, periprosthetic joint infection; DAIR, debridement, antibiotics and implant retention; SAT, suppressive antimicrobial therapy; IDSA, Infectious Diseases Society of America.
Except for the therapeutic dose subgroup, all pooled success rates showed relevant between study variation (heterogeneity) of more than 40%.
[a]One study (Kildow), included both acute and chronic PJI but reported patient outcome for these two groups separately.
[b]One study (Hanssen) individual patient data on chronic PJI was available.
[c]all patients who stopped SAT combined; both pre-emptively planned to stop as those who stopped for example due to side effects or because physicians believed the patient was cured.

Assessment of publication bias

The funnel plot showed a broad, symmetrical distribution of studies, consistent with the substantial between-study variation (Supplementary Figure 1). Trim-and-fill analysis detected no missing studies and did not alter the pooled estimate.

Definition of SAT

Reported definitions in included literature

Most studies (n=23) did not report a definition of SAT. Definitions were heterogeneous, typically one or more of three aspects differed: (1) the starting point of SAT (i.e., the transition from therapeutic to suppressive treatment), (2) the intended duration (fixed, indefinite, or lifelong), and (3) the treatment goal (curative versus non-curative). Supplementary table 6 contains all reported definitions from included studies.

In the U.S. literature, eight studies provided a definition. Of these, seven studies defined the starting point, four the intended duration, and one the treatment goal as

part of the definition. In the remaining U.S. studies, any prolonged oral antibiotic use in PJI was referred to as "SAT" or "chronic suppression". Eleven studies from Europe provided a definition. Five defined the starting point, seven the intended duration (six: indefinite/lifelong, one: treatment over six months), and six the treatment goal as part of the definition.

SAT definition by modified Delphi process

To address the substantial heterogeneity in how SAT was defined across the included studies, all components of the reported definitions were extracted and subsequently refined through the modified Delphi procedure described in the Methods section. This process yielded final consensus definitions of *suppressive antimicrobial therapy* (SAT) and the related term *extended antimicrobial therapy* (EAT). Agreement among panel members for individual definitional components ranged from 78% to 100%, with full consensus ultimately achieved on the final definitions (table 2).

Table 2. Consensus Definitions for Suppressive and Extended Antimicrobial Therapy in Periprosthetic Joint Infection.

Suppressive antimicrobial therapy (SAT):
A non-curative antimicrobial regimen continued beyond the recommended therapeutic treatment duration according to (inter)national guidelines, with the goal of suppressing a latent infection (i.e., preventing symptoms and potential consequences thereof).
a. When prescribed indefinitely, SAT is intended to be continued without a planned stop, because curative surgery will not be performed.
b. When prescribed for a fixed term, SAT is intended to be discontinued once conditions have improved to allow for curative surgery.
Extended antimicrobial therapy (EAT):
A curative-intent antimicrobial regimen continued for a fixed term beyond the recommended therapeutic treatment duration according to (inter)national guidelines to increase the likelihood of infection eradication without additional surgery.

Discussion

The need for a standardized definition of SAT

This review demonstrates that the commonly used term 'SAT' in PJI literature refers to varying treatment strategies used in heterogenous patient populations. This lack of conceptual uniformity complicates interpretation of reported outcomes and limits comparability between studies, underscoring the need for a standardized definition of SAT. Importantly, long-term antimicrobial therapy may be used both in situations where cure remains the goal of treatment and in situations where cure is unlikely and treatment is intended to suppress infection. By distinguishing suppressive an-

timicrobial therapy from extended antimicrobial therapy with curative intent, the consensus definitions proposed in this study aim to improve clarity in future research and facilitate more consistent reporting of treatment strategies and outcomes.

Treatment duration

For chronic PJI managed without exchange arthroplasty, SAT was usually prescribed indefinitely. However, two studies reported that even in this high-risk population, discontinuing SAT after two years did not result in worse outcomes compared to indefinite therapy . In clinical practice, discontinuation of SAT (regardless of the indication) after several years is relatively common both in Europe, the U.S. and Oceania, yet criteria for cessation remain poorly defined and largely clinician- or patient-driven (1).

Whether extending antimicrobial therapy beyond 12 weeks is beneficial for acute PJI treated with DAIR without risk factors for failure remains debated. Also, the optimal duration of such prolonged treatment is uncertain. Antimicrobial treatment beyond one or two years did not further improve failure-free survival in observational studies.

Overall, establishing objective criteria for discontinuing long-term antibiotics and identifying which patients may safely stop therapy remain important unresolved clinical challenges.

Outcome

The overall pooled success rate of SAT (74%) appeared relatively high compared with succes rates reported in the literature after DAIR (55–90%) or revision surgery (≈85%) (8-10). Success rates were equal for acute PJI managed with DAIR and chronic PJI treated with DAIR or without surgery. However, these findings should be interpreted with caution, as reported success rates are strongly influenced by study methodology and patient selection, and should not be interpreted as reflecting treatment efficacy alone. Definitions of treatment failure differed considerably across studies and such heterogeneity in outcome definitions affects pooled estimates. In addition, patients selected for SAT are typically clinically stable and able to tolerate prolonged therapy, introducing selection and survivorship bias that may inflate reported success rates. Of note, in other studies on PJI (outside the scope of this review), initiation of SAT is sometimes classified as treatment failure or treated as a competing endpoint rather than as a therapeutic strategy, further complicating interpretation of SAT outcomes.

Australasian perspective

A prospective PJI cohort study from Australia and New Zealand, published after completion of our literature search, provides additional insight of contemporary SAT

practice from a different region (11). In this study (n = 720), SAT was prescribed in 31% of patients, predominantly in those who were older, comorbid, had chronic PJI, a sinus tract, or were managed with DAIR or without surgery. SAT was defined as therapy extending beyond 12 months or initiated with an early intent for long-term suppression. The goals were symptom control and avoidance of further surgery rather than cure. SAT was associated with failure (adjusted OR 2.5, 95% CI 1.7–3.7), likely reflecting confounding by indication. These findings further illustrate the heterogeneity in SAT practice internationally and highlight the need for clear definitions and risk stratification in future studies.

Framework for future SAT research

Taken together, the present review demonstrates that —beyond the absence of a uniform definition of SAT—interpretation of SAT data is further complicated by heterogeneous study populations and varying outcome definitions. The observed differences between U.S. and European studies should be interpreted with caution though. As our review was designed to synthesize data from studies on PJI treated with SAT rather than DAIR management more broadly, we did not collect data on patients undergoing DAIR without SAT. The categories presented in Figure 2 therefore reflect how study populations and indications were described in the included reports, rather than representing how patients treated with DAIR are generally managed (i.e., with or without SAT). While clinical decision-making is usually more nuanced than reflected in published reports, our findings highlight differences in the types of SAT populations studied in the existing literature. Stratifying patients according to relapse risk may therefore enable a more individualized interpretation of SAT strategies and improve the translation of study findings to clinical practice. We therefore propose an expert opinion-based risk classification based on expected relapse risk if SAT would be withheld, with elements partly adapted from the European Bone and Joint Infection Society (EBJIS) position paper on DAIR as curative strategy for acute periprosthetic hip and knee infection (Fig 3) (5).

Low risk	Medium risk	High risk	Very high risk	Indeterminate
PJI treated with exchange arthroplasty PJI treated with DAIR under the following conditions: • Well-fixed prosthesis • Acute PJI: – Early acute: ≤4 weeks after index arthroplasty – Late acute: < 3 weeks of symptoms after an uneventful postoperative period • Good conditions of the surrounding soft tissue without a sinus tract	PJI treated with DAIR with the following risk factors: • Early acute: 4–12 weeks after index arthroplasty • Multiple previous revision surgeries • Host and clinical factors: – Rheumatoid arthritis – COPD – Immunosuppressive therapy • *S. aureus* infection (late acute PJI) • Difficult to treat microorganism – no biofilm active antimicrobial therapy available – and fungal infections • Bacteraemia	PJI treated with DAIR despite not recommended due to: • Loose prosthesis • > 12 weeks after index arthroplasty • > 3 weeks of symptoms • Presence of a sinus tract • Compromised soft tissue	PJI treated without surgery – antimicrobial treatment only	Low-risk profile, but SAT started because of old age or frailty

Figure 3. *Expert opinion-based classification of risk for failure in patients receiving SAT*. *This classification can be used for research purposes and is adapted from the European Bone and Joint Infection Society (EBJIS) position paper on debridement, antimicrobial therapy, and implant retention (DAIR) as a curative strategy for acute periprosthetic hip and knee infection (5). The "very high-risk" (purple column) and "indeterminate" (blue column) categories were added based on the current systematic review. Patients are classified according to the highest risk factor present; the presence of a single factor in a given column places the patient in that risk category.*

This proposed classification aligns with clinical practice and is feasible for research purposes. The EBJIS position paper was not intended to provide a formal risk stratification, but it offers a comprehensive overview of risk factors for DAIR failure, which makes it a useful reference for the proposed classification. Stratifying patients by risk profile is essential, as the likelihood of persistent biofilm and relapse after initial treatment varies across these groups. In addition to risk stratification, interpretation of SAT success also depends on patient preferences. In frail patients prioritizing symptom control and avoidance of surgery, long-term suppression may represent a favorable outcome. Conversely, in younger or surgically fit patients, continued SAT may be less desirable compared with curative strategies. Incorporating Desirability of Outcome Ranking frameworks in future studies would further strengthen evaluation of SAT by explicitly integrating clinical context and treatment goals.

Strengths and limitations

This systematic review is the first to comprehensively evaluate definitions and practices of SAT and included the largest number of studies on SAT in PJI to date. Strengths include a comprehensive literature search, combined qualitative and quantitative analysis, and practical recommendations for SAT definitions and patient stratification.

Limitations include the heterogeneity in study design and patient populations, variability in outcome reporting, and the overall low methodological quality of the included studies according to the MINORS tool, indicating a considerable risk of bias. Not all data were extracted in duplicate; however, verification of a random sample of 25% of the included studies did not reveal discrepancies. Since our literature search specifically targeted suppressive therapy, we may have missed studies on long-term antibiotic treatment for PJI that did not explicitly label their approach as SAT. Moreover, in our qualitative synthesis of SAT indications and patient populations, we primarily captured chronicity-based indications, whereas other potential risk factors such as host immunocompromise, specific pathogens, or local surgical complexity were not always systematically reported and therefore not analyzed in detail. Lastly, the expert panel comprised more European than American or Australian participants, which may have influenced the consensus-derived definition.

Conclusion

Definitions and reported practices of suppressive antimicrobial therapy for PJI vary widely. This complicates data interpretation and hampers communication among clinicians and researchers. Implementation of standardized definitions and risk-based patient stratification will improve research comparability, enable better clinical decision-making, and allow more accurate assessment of SAT effectiveness and treatment strategies in distinct patient populations.

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Supplement

Supplementary Table 1. Search strategy

Databases:	Pubmed, Embase
Search terms:	("prosthetic joint infection*"[tiab] OR "prosthetic joint infection"[tiab:~2] OR "prosthetic joint infections"[tiab:~2] OR "PJI"[tiab] OR "arthroplast*"[tiab] OR "implant-related"[tiab] OR "implant related"[tiab] OR "periprosthetic joint infection*"[tiab] OR "peri-prosthetic joint infection*"[tiab] OR "arthroplasty"[mesh] OR "Prosthesis-Related Infections"[Mesh] OR "prosthesis-related infection*"[tiab] OR "prosthesis-related infection"[tiab:~2] OR "prosthesis-related infections"[tiab:~2]) AND ("suppress*"[tiab] OR "prolonged antibiotic"[tiab] OR "extended antibiotic"[tiab] OR "SAT"[tiab] OR "long term antibiotic"[tiab] OR "chronic antibiotic"[tiab] OR "lifelong antibiotic"[tiab])

Supplementary Table 2. MINORS Item-by-Item Assessment of Included Studies

author	1.	2.	3.	4.	5.	6.	7.	8.	9.	10.	11.	12.	Total Score
Barry	2	2	1	2	0	2	1	0	2	2	1	1	16/24
Bene	2	2	1	1	0	2	2	0	-	-	-	-	10/16
Bene	2	2	1	1	0	2	2	0	-	-	-	-	10/16
Brandt	2	0	1	2	0	2	1	0	-	-	-	-	8/16
Bryan	2	2	1	2	0	2	2	0	-	-	-	-	11/16
Burr	2	2	1	1	0	2	2	0	-	-	-	-	10/16
Byren	2	2	1	2	2	2	1	0	-	-	-	-	12/16
Ceccarelli	2	0	1	1	0	1	2	0	-	-	-	-	7/16
Chao	2	0	2	2	0	2	2	0	2	1	1	2	16/24
Dos Santos	2	0	2	2	1	2	1	0	2	1	2	2	17/24
Escudero-Sanchez	2	0	1	2	1	2	2	0	-	-	-	-	10/16
Ferry	1	0	2	2	0	1	2	0	-	-	-	-	8/16
Furukawa	2	2	0	1	0	2	2	0	1	2	2	1	14/24
Goulet	1	0	0	1	0	2	2	0	-	-	-	-	6/16
Goutelle	1	0	1	1	0	1	2	0	-	-	-	-	6/16
Hanssen	2	0	2	2	0	1	2	0	-	-	-	-	9/16
Huotari	2	0	2	2	0	1	2	0	-	-	-	-	9/16
Kherabi	2	2	2	2	0	2	2	0	-	-	-	-	11/16
Kildow	2	0	2	2	0	2	2	0	-	-	-	-	10/16
Koeppe	2	0	0	1	0	2	2	0	-	-	-	-	7/16
Lafon	1	0	0	0	0	1	2	0	-	-	-	-	4/16
Leijtens	2	0	0	2	0	1	2	0	-	-	-	-	7/16
Lensen	2	0	2	2	0	1	2	0	2	2	1	1	15/24
Marculescu	2	0	2	2	0	2	2	0	-	-	-	-	10/16
Nandi	2	2	2	2	0	2	2	0	-	-	-	-	10/16
Pradier	2	0	2	2	0	2	2	0	2	1	2	1	16/24
Prendki ('14)	2	0	2	2	0	2	2	0	-	-	-	-	10/16
Prendki ('17)	2	0	2	2	0	2	1	0	-	-	-	-	9/16
Rao	2	0	2	2	0	2	1	0	-	-	-	-	9/16
Salmons	2	0	2	2	0	2	2	0	-	-	-	-	10/16
Sandiford	2	0	2	2	0	2	2	0	-	-	-	-	10/16
Segreti	2	0	0	2	0	2	2	0	-	-	-	-	8/16
Shah	2	0	2	2	0	2	2	0	2	0	1	2	15/24
Siquera	2	2	2	2	0	2	2	0	2	2	2	2	20/24
Spichler	2	0	2	1	0	1	2	0	-	-	-	-	8/16
Tai ('22)	2	0	2	2	0	2	2	0	-	-	-	-	8/16
Tai ('24)	2	0	2	2	0	2	2	0	1	2	1	2	16/24
Vahedi	2	0	2	2	0	1	2	0	1	0	2	1	13/24

Supplementary Table 2. MINORS Item-by-Item Assessment of Included Studies *(Continued)*

author	1.	2.	3.	4.	5.	6.	7.	8.	9.	10.	11.	12.	Total Score
Valencia	2	0	2	2	0	2	1	0	2	0	0	2	13/24
Weston	2	0	2	2	0	2	1	0	-	-	-	-	9/16
Wolff	2	0	0	1	0	2	2	0	-	-	-	-	7/16
Wouthuyzen	2	0	2	2	0	1	2	0	-	-	-	-	9/16

-: not applicable. *The items are scored 0 (not reported), 1 (reported but inadequate) or 2 (reported and adequate). The global ideal score being 16 for non-comparative studies and 24 for comparative studies.

Items of MINORS

Methodological items for non-randomized studies

(1) A clearly stated aim: the question addressed should be precise and relevant in the light of available literature.

(2) Inclusion of consecutive patients: all patients potentially fit for inclusion (satisfying the criteria for inclusion) have been included in the study during the study period (no exclusion or details about the reasons for exclusion).

(3) Prospective collection of data: data were collected according to a protocol established before the beginning of the study.

(4) Endpoints appropriate to the aim of the study: unambiguous explanation of the criteria used to evaluate the main outcome, which should be in accordance with the question addressed by the study. Also, the endpoints should be assessed on an intention-to-treat basis.

(5) Unbiased assessment of the study endpoint: blind evaluation of objective endpoints and double-blind evaluation of subjective endpoints. Otherwise, the reasons for not blinding should be stated.

(6) Follow-up period appropriate to the aim of the study: the follow-up should be sufficiently long to allow the assessment of the main endpoint and possible adverse events.

(7) Loss to follow-up less than 5%: all patients should be included in the follow-up. Otherwise, the proportion lost to follow-up should not exceed the proportion experiencing the major endpoint.

(8) Prospective calculation of the study size: information on the size of detectable difference of interest with a calculation of 95% confidence interval, according to the expected incidence of the outcome event, and information about the level for statistical significance and estimates of power when comparing the outcomes.

Additional criteria in the case of comparative study

(9) An adequate control group: having a gold standard diagnostic test or therapeutic intervention recognized as the optimal intervention according to the available published data.

(10) Contemporary groups: control and studied groups should be managed during the same time period (no historical comparison).

(11) Baseline equivalence of groups: the groups should be similar regarding the criteria other than the studied endpoints. Absence of confounding factors that could bias the interpretation of the results.

(12) Adequate statistical analyses: whether the statistics

Supplementary Table 3. Reported definitions of SAT failure (n=42)

Author	year	region	Reported definition of SAT failure
Goulet	1988	US	Not reported
Brandt	1996	US	relapse of S. aureus PJI or occurrence of culture-negative PJI during continuous antistaphylococcal therapy
Segreti	1998	US	removal or revision of their prostheses, sepsis
Rao	2003	US	the development of progressive pain, loosening of the implant, or drainage despite antibiotic therapy.
Wolff	2003	US	recurrence of infection
Marculescu	2006	US	Occurrence of a PJI due to the original microorganism at any time after the surgical procedure (relapse of infection); Occurrence of a PJI due to a different strain or different microorganism (reinfection) at any time after the surgical procedure; Presence of acute inflammation in the periprosthetic tissue on histopathological examination or at any subsequent surgery on the joint; Development of a sinus tract; Death from prosthesis-related infection;
Koeppe	2008	US	loss of a functional prosthesis due to infection.
Siquera	2015	US	subsequent surgical intervention for infection after the index procedure; (2) persistent fistula, drainage, or joint pain at the last follow-up visit; or (3) death related to the periprosthetic joint infection.

Supplementary Table 3. Reported definitions of SAT failure (n=42) *(Continued)*

Author	year	region	Reported definition of SAT failure
Bryan	2017	US	failure to eradicate infection characterized by a wound fistula, drainage, intolerable pain, or infection recurrence caused by the same organism strain; subsequent removal of any component for infection; unplanned second wound debridement for ongoing deep infection; and/or occurrence of periprosthetic joint infection-related mortality,
Weston	2018	US	subsequent or recurrent infection
Bene	2018	US	reoperation for infection recurrence
Bene	2018	US	reoperation for infection recurrence
Vahedi	2019	US	reinfection
Valencia	2019	US	Fulfilling the Musculoskeletal Infection Society criteria for PJI
Barry	2020	US	reoperation for infection)
Shah	2020	US	occurrence of PJI that occurred any time after the primary antibiotic therapy period, as well as any further surgical procedure on the operative knee due to infection
Kildow	2021	US	occurrence of PJI that occurred any time after the primary antibiotic therapy period, as well as any further surgical procedure on the operative knee excluding manipulation under anesthesia, periprosthetic fracture, and extensor mechanism disruption.
Tai	2022	US	(1) recurrence of PJI as defined, (2) unplanned reoperation (DAIR, implant resection, amputation) secondary to infection, or (3) infection-related death.
Burr	2022	US	reoperation after starting CAS therapy or if they died of causes directly related to their PJI.
Spichler	2023	US	Not reported
Salmons	2023	US	any reoperation for infection
Tai	2024	US	recurrence of PJI, unplanned reoperation secondary to infection, or infection-related death
Nandi	2024	US	reoperation for infection recurrence
Furukawa	2024	US	repeat surgery for clinical suspicion of infection leading to repeat treatment with a prolonged course of antibiotics
Chao	2024	US	occurrence of PJI, based on the modified MSIS criteria, that occurred any time after the primary antibiotic therapy period as well as any further surgical procedure on the operative knee, due to infection
Byren	2009	Europe	infection recurrence with positive cultures from peri-prosthetic samples or an aspirate; wound or sinus drainage recurring or persisting for 3 months beyond the index debridement procedure; or a requirement for revision surgery
Prendki	2014	Europe	persisting infection, relapse, new infection, treatment discontinuation because of severe adverse events, or related death
Prendki	2017	Europe	(i) local or systemic progression of the infection (failure), (ii) death and (iii) discontinuation or switch of PSAT

Supplementary Table 3. Reported definitions of SAT failure (n=42) *(Continued)*

Author	year	region	Reported definition of SAT failure
Wouthuyzen	2017	Europe	1) the patient still reported joint pain during follow-up visits at the outpatient clinic, 2) when surgical intervention was needed to control the infection (i.e. removal of the prosthesis (Girdlestone or arthrodesis), revision surgery and/or amputation/ dysarticulation) and/or 3) when death occurred due to the infection
Pradier	2018	Europe	signs of infection
Leijtens	2019	Europe	death related to PJI or new surgical intervention at prosthesis side due to persistent or recurrent infection
Escudero	2020	Europe	no admissions due to sepsis arising from the affected joint; no progression to further surgery or death from related causes
Sandiford	2020	Europe	appearance or persistence of a fistula, the need for debridement or replacement of the prosthesis due to persistence of the infection or the presence of uncontrolled symptoms. OR PJI related death
Goutelle	2021	Europe	Not reported
Ferry	2021	Europe	the presence of clinical signs suggestive of uncontrolled infection and the need for a new surgical procedure.
Lensen	2021	Europe	Failure of: retention of the implant during follow-up. Secondary end points consisted of failure of: the prevention of prosthetic loosening in initially fixed implants, the need for surgical debridement during follow-up, closing of the sinus tract, resolution of pain, the development of bacteremia, the resolution of inflammation and anaemia, and side ffects when treated with SAT
Kherabi	2022	Europe	Reinfection
Huotari	2023	Europe	No removal of the implant, no infection-related death, or active infection at the end of follow-up
Ceccarelli	2023	Europe	severe joint pain, warmth, redness, tenderness, effusion, restricted active and passive motion, and presence of new fistula or local dehiscence or decubitus. Fever and signs of sepsis were considered indicators of possible systemic spread through bacteremia. Additionally, a new positive result of the LS was considered a sign of failure
Hanssen	2024	Europe	the appearance or persistence of a fistula, unplanned surgical intervention or admission for IV antibiotics, increasing the low-dosage SAT to standard dosage, restart of antimicrobial treatment after stopping SAT, uncontrolled symptoms, or death related to the infection
Lafon	2024	Europe	Not reported
Dos Santos	2025	Europe	(i) sinus tract and/or discharge, and signs of PJI recurrence, (ii) further surgical intervention for persistent or perioperative infection, (iii PJI-related death within 3 months

Supplementary Table 4. Studies on SAT that reported an outcome of SAT (n=40)

author	year	region	N	N acute	N chronic	% DAIR	duration SAT (months)	follow-up (months)	Success rate (%)
Goulet	1988	US	19	2	17	58	48 (mean)	48 (mean)	63
Brandt	1996	US	18	n.a.	n.a.	100	n.a.	78 (median)	39
Segreti	1998	US	18	8	10	100	49 (mean)	n.a.	83
Siquera	2015	US	92	n.a.	n.a.	59	64 (mean)	69 (mean)	65
Bryan	2017	US	69	69	0	100	72 (mean)	72 (mean)	97
Bene	2018	US	76	76	0	100	12 (mean)	42 (mean)	72
Bene	2018	US	26	26	0	100	20 (mean)	49 (mean)	92
Weston	2018	US	129	129	0	100	n.a.	60 (mean)	66
Vahedi	2019	US	24	24	0	100	n.a.	46 (mean)	71
Valencia	2019	US	11	n.a.	n.a.	0	36 (median)	31 (median)	91
Shah	2020	US	51	17	34	100	28 (median)		69
Barry	2021	US	56	41	15	100	n.a.	37 (median)	63
Kildow	2021	US	35	26	9	100	16 (mean)	17(mean)	80
Burr	2022	US	45	0	45	0	50 (median)	50 (median)	67
Tai	2022	US	227	170	57	100	25 (median)	48 (median)	78
Salmons	2023	US	40	40	0	100	84 (mean)	84 (mean)	68
Chao	2024	US	35	35	0	100	12	36	61
Furukawa	2024	US	90	63	27	100	6 (median)	27 (median)	89
Nandi	2024	US	115	115	0	100	11 (median)	33 (mean)	77
Tai	2024	US	167	167	0	100	n.a.	27 (median)	77
Byren	2009	Europe	112	93	19	100	18 (mean)	28 (mean)	82
Prendki	2014	Europe	38	15	23	18	24 (median)	24 (median)	84
Prendki	2017	Europe	136	n.a.	n.a.	58	6 (median)	6 (median)	93

Supplementary Table 4. Studies on SAT that reported an outcome of SAT (n=40) *(Continued)*

author	year	region	N	N acute	N chronic	% DAIR	duration SAT (months)	follow-up (months)	Success rate (%)
Wouthuyzen	2017	Europe	21	n.a.	n.a.	29	21 (median)	21 (median)	67
Pradier	2018	Europe	78	n.a.	n.a.	76	22 (mean)	34 (mean)	78
Leijtens	2019	Europe	23	0	23	44	38 (mean)	33 (median	57
Escudero	2020	Europe	302	82	220	56	36,5(median)	37 (median)	59
Sandiford	2020	Europe	24	n.a.	n.a.	65	37 (mean)	38 (mean)	83
Goutelle	2021	Europe	10	0	10	n.a.	34 (median	34 (median)	80
Ferry	2021	Europe	16	0	16	81	6 (median)	8 (median)	75
Lensen	2021	Europe	63	0	63	0	54 (mean)	54 (mean)	79
Kherabi	2022	Europe	31	n.a.	n.a.	0	13	13	84
Ceccarelli	2023	Europe	11	0	11	100	21 (median)	n.a.	64
Huotari	2023	Europe	22	22	0	100	n.a.	n.a.	100
Hanssen	2024	Europe	67	28	39	79	20 (median)	22 (median)	60
Dos Santos	2025	Europe	30	13	17	43	42 (median)	48 (median)	73

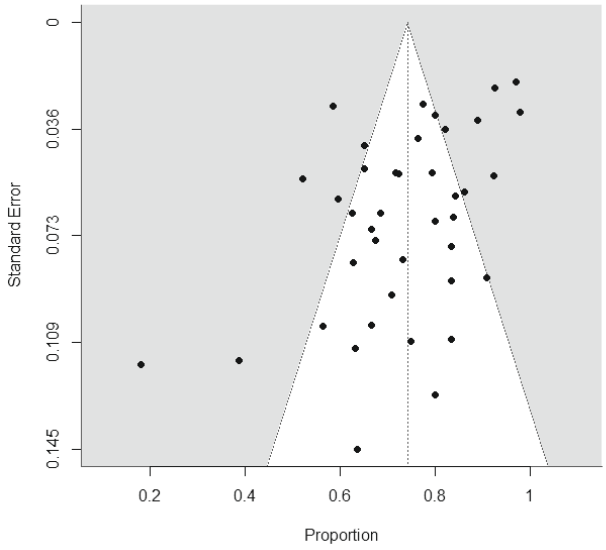
Supplementary Table 5. Studies Comparing SAT versus No SAT in Patients with PJI Treated with DAIR (n=8)

author	year	region	N SAT	% acute PJI, SAT	% DAIR	N no SAT	% acute PJI, no SAT	% DAIR, no SAT	Success rate SAT (%)	Succes rate, no SAT (%)	P
Brandt	1996	US	18	n.a.	100	15	n.a.	100	39	33	0.79
Siquera	2015	US	54	n.a.	100	152	n.a.	100	65	30	<0.01
Bryan	2017	US	69	100	100	9	100	100	97	89	0.3
Shah	2020	US	51	n.a.	100	57	n.a.	100	69	39	0.009
Chao	2024	US	35	100	100	39	100	100	65[a]	38[a]	0.02
Tai	2024	US	167	100	100	343	100	100	77	92	0.27
Huotari	2023	Europe	22	100	100	61	100	100	100	74	n.a.
Dos Santos	2025	Europe	30	43	43	33	24	24	73	42	0.02

[a]Survival probability at 24 months

Supplementary Table 6. Studies on SAT that reported a definition of SAT

Author	year	region	Reported definition
Brandt	1996	US	oral antimicrobial therapy of indefinite duration following the completion of iv antimicrobial therapy
Marculescu	2006	US	Orally administered antimicrobial therapy of indefinite duration received after completion of intravenous antimicrobial therapy
Koeppe	2008	US	use of oral antibiotics for the prevention of relapse, rather than the treatment of the underlying infection. It is assumed in these patients that the prosthesis remains infected, and oral antibiotics are given indefinitely to keep the symptoms under control but not cure the infection.
Siquera	2015	US	treatment with oral antibiotics for a minimum of six months following the initial course of intravenous antibiotics.
Shah	2020	US	any antibiotics that were provided beyond 6 weeks after DAIR
Burr	2022	US	chronic control clinical symptoms rather than to cure infection.
Chao	2024	US	Extended antibiotic therapy included any oral antibiotics that were provided beyond 6 weeks for one year after the initial DAIR procedure.
Tai	2024	US	antibiotic therapy after 12 weeks of therapy
Furukawa	2024	US	oral antibiotics given after completion of IV therapy.
Prendki	2014	Europe	an oral antibiotic therapy prescribed for a duration longer than a curative treatment
Prendki	2017	Europe	an antimicrobial therapy with a lifelong planned duration, even if it could be secondarily discontinued by the physician in charge of the patient.
Wouthuyzen	2017	Europe	antibiotic treatment that was started after the standard 3 months of 'regular' antibiotic treatment (in most cases 2 weeks of intravenous therapy and 10 weeks of oral therapy)
Pradier	2018	Europe	oral antibiotic therapy following curative therapy
Leijtens	2019	Europe	oral antibiotic therapy without an end date, started with the intention to control the infection where curative treatment seems unachievable
Escudero-Sanchez	2020	Europe	indefinite administration of antibiotics with a non-curative intention, in the context of either a PJI for which cure would require complete removal of the implant (as occurs for late chronic infections) or an acute infection for which conservative treatment such as DAIR has failed.
Sandiford	2020	Europe	oral antibiotic therapy continuing beyond 12 weeks with an intention to continue lifelong as documented at the time of starting therapy.
Ferry	2021	Europe	indefinite administration of antibiotics without curative intention in the context of a chronic infection that would normally require implant removal;
Lensen	2021	Europe	a period of >6 months of oral antibiotic therapy.
Ceccarelli	2023	Europe	a strategy based on a suppressive antibiotic treatment in which the administration of antibiotics occur in the long term or indefinitely over time with the aim of reducing symptoms and delaying or preventing the progression of PJI in cases not eligibile for standard surgical treatment
Hanssen	2024	Europe	prolonged oral antimicrobial therapy after the initial standard treatment of 6 to 12 weeks.



Supplementary Figure 1. Funnel plot assessing publication bias among the included studies

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Chapter 7

Dosing and treatment duration of suppressive antimicrobial therapy in orthopedic implant infections: a cohort study

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Abstract

Introduction*:* Limited data inform about the optimal dosing and duration of suppressive antimicrobial therapy (SAT) for orthopedic implant infections (OII). We aimed to compare the effectiveness of low dosage with standard dosage SAT and evaluate the safety of stopping SAT.

Methods*:* All patients with OII treated with SAT from 2011 to 2022 were retrospectively included. Data were extracted from electronic patient files. Low dosage SAT was defined as antimicrobial therapy dosed lower than the standard dosage recommended for OII. The association of dosing strategy and other factors with failure-free survival were assessed by Kaplan-Meier and Cox proportional hazards models.

Results: One-hundred-and-eight patients were included. The median follow up time after SAT initiation was 21 months (IQR 10–42 months). SAT was successful in 74 patients (69 %). Low dosage SAT (n = 82) was not associated with failure in univariate (hazard ratio (HR) 1.23, 95 % confidence interval (CI) 0.53–2.83) and multivariate analysis (HR 1.24, 95 % CI 0.54–2.90). In 25 patients (23 %) SAT was stopped after a median treatment duration of 26 months. In this group, one patient (4 %) developed a relapse.

Conclusions: In this study, low dosage SAT was as effective as standard dosage SAT. Moreover, stopping SAT after two to three years may be justified in patient with a good clinical course. These findings warrant further research on optimal dosing and duration of SAT and on the durability of in vivo biofilms.

Introduction

Patients with orthopedic implant infection (OII) managed with implant retention and a high likelihood of relapse after initial treatment often receive chronic suppressive antimicrobial therapy (SAT). Reported success rates of this strategy vary between 23 % and 95 % and the preferred regimen, dosage and treatment duration of SAT differ around the world (Cobo and Escudero-Sanchez, 2021).

With respect to the dosage, the 2013 Infectious Diseases Society of America (IDSA) guideline suggests that antibiotics can be lowered for SAT compared to the standard prosthetic joint infection (PJI) treatment dosages (Osmon et al., 2013). Studies specifically addressing low dosage SAT have not been published, although low dosage SAT is mentioned in several studies (Siqueira et al., 2015; Bryan et al., 2017; Prendki et al., 2017; Wouthuyzen-Bakker et al., 2017).

Another important clinical question is whether SAT can ever be discontinued and if so, based on which clinical criteria. The IDSA guideline recommends indefinite oral SAT in patients with PJI who qualify for SAT (Osmon et al., 2013). Most studies on SAT for PJI also reported the duration of suppression to be lifelong (Prendki et al., 2017; Wouthuyzen-Bakker et al., 2017; Pradier et al., 2018; Escudero-Sanchez et al., 2020).

Over the years, it became common practice in our hospital to treat patients on SAT with a dosage that is lower than the standard (i.e. therapeutic) dosage used in the treatment of OII. This was believed to be a reasonable approach due to the presumed low bacterial load after the initial antibiotic treatment period combined with our clinical experience that lowering the dosage of SAT in patients (due to side effects) did not result in more relapses. Further, SAT was increasingly being stopped after two to three years in patients with good clinical performance rather than continuing with suppression indefinitely. The aim of this study was to analyze the clinical outcomes of this treatment strategy for OII.

Methods

Study design and population

This retrospective observational study was conducted in a tertiary care hospital in the Netherlands. The inclusion period ranged from June 1st, 2011 to November 1st, 2022. All consecutive patients with PJI, fracture related infection (FRI) and spinal implant infection (SII) who started on SAT were eligible for inclusion. These eligible partic-

ipants were identified using CTcue text mining software (IQVIA B.V., Amsterdam, The Netherlands). Clinical data were manually extracted after patient file review by a single researcher (J.L.J.H.) who consulted one of the senior co-authors (M.G.J.d.B. or H.S.) when in doubt of a case. H.S. validated data from a random set of cases (10 % of total). Exclusion criteria were age < 16 years, follow-up less than one month from start SAT and unlikely PJI according to the European Bone and Joint infection Society (EBJIS) criteria (Mcnally et al., 2021). Follow-up time started on the first day of SAT.

Standard management of OII

Since 2015, a multidisciplinary team was implemented that discussed all patients with OII during weekly meetings. Team members were orthopedic and trauma surgeons, infectious diseases specialists and clinical microbiologists. Standard management of OII consisted of debridement, antibiotics and implant retention (DAIR) for acute OII and revision surgery in combination with antibiotics for chronic OII, unless specific conditions dictated otherwise. All study participants were treated with surgical debridement unless a contra-indication for surgery existed or if the patient refused surgery. Antimicrobial treatment consisted of one to two weeks of intravenous (iv) antibiotics followed by four to 11 weeks of targeted oral antimicrobial therapy (for a total duration of six to 12 weeks). The decision to start SAT after the initial therapeutic antimicrobial treatment episode was made by the MDT and based on the resolution of symptoms and normalization of inflammatory parameters. Besides the scheduled cessation of SAT in case of good clinical performance, suppression could also be stopped if unacceptable side effects to antibiotics arose or if this was requested by the patient.

Study definitions

PJI and FRI were defined according to 2021 EBJIS definitions (Govaert et al., 2020; Mcnally et al., 2021). The PJI criteria were also applied to SII due to lack of specific diagnostic criteria for SII. For this study, SAT was defined as prolonged oral antimicrobial therapy after the initial standard treatment of six to 12 weeks. Low dosage SAT was defined as antimicrobial treatment that was lower or less frequently dosed than the oral therapeutic dosage (standard dosage SAT) recommended for the treatment of OII in our hospital. The dosages used in this study are summarized in Table 1.

Table 1 Dosing schedules of suppressive antimicrobial therapy in the standard dosage group and in the low dosage group in this study.

	standard dosage SAT	low dosage SAT
Amoxicillin	1000 mg t.i.d. or q.i.d.	500 mg b.i.d., t.i.d. or q.i.d. 1000 mg b.i.d
Flucloxacillin	1000 mg q.i.d.	500 mg b.i.d, t.i.d. or q.i.d. 1000 mg b.i.d. or t.i.d.
Amoxicillin/clavulanic avid	1250 mg t.i.d.	625 mg b.i.d
Feneticillin	1000 mg q.i.d.	500 mg q.i.d.
Ciprofloxacin	500–750 mg b.i.d.	500–750 mg q.d.
Levofloxacin	500 mg b.i.d.	250-500 mg q.d.
Moxifloxacin	400 mg q.d.	-
Clindamycin	600 mg t.i.d.	300 mg b.i.d. or t.i.d. 600 mg b.i.d.
Trimethoprim-sulfamethoxazole	960 mg b.i.d.	480 mg q.d or b.i.d. 960 mg q.d..
Doxycycline	100 mg b.i.d.	100 mg q.d.
Linezolid	600 mg b.i.d.	150–600 mg q.d.
Rifampicin[a]	450–600 mg b.i.d.	300 mg q.d.
Fluconazole	200 mg b.i.d.	200 mg q.d.

The abbreviations used in the table are as follows: SAT - suppressive antimicrobial therapy; q.d. – once daily; b.i.d. – twice daily; t.i.d. – three times a day; q.i.d. – four times a day. [a] In combination with levofloxacin

Patients were categorized into two groups: a low dosage group and a standard dosage group. OIIs were classified as early postoperative (less than three months after surgery), late chronic (symptoms more than three weeks and diagnosis more than three months after surgery) and acute hematogenous (symptoms less than three weeks in a previously asymptomatic patient at least 3 months after surgery).

For the purpose of this study, we retrospectively defined two indications for SAT: i. "Certain" relapse (without SAT): OII treated without any surgery, late chronic infection treated with DAIR or acute infection with failure of DAIR, ii. "High risk" of relapse (without SAT): early postoperative and acute hematogenous OII treated with DAIR in the presence of at least one of the following risk factors for relapse: tumor endoprosthesis, previous failures, poor soft tissue and/or bone stock, significant comorbidity (e.g. on chemotherapy, active rheumatoid arthritis) and difficult-to-treat microorganisms (e.g. *Candida albicans*) (Cobo and Escudero-Sanchez, 2021).

Failure was defined as one of the following outcomes: the appearance or persistence of a fistula, unplanned surgical intervention or admission for iv antibiotic, increasing low dosage SAT to standard dosage, restart of antimicrobial treatment after stopping

SAT, uncontrolled symptoms and death related to the infection. SAT was considered successful if none of these events occurred. Endpoints were failure, death unrelated to OII or latest follow-up at the outpatient clinic when no event occurred.

Statistical analysis

Continuous variables were described as means with 95 % confidence intervals (CI) or as medians with interquartile ranges (IQR). Normally distributed data was compared between groups using Students' t-test and non-normally distributed data with Mann Whitney U test. Categorical variables were compared with the chi-square test or with Fisher's exact test if more than 20 % of cells had expected frequencies less than five. The primary outcome was treatment failure-free survival time, assessed by Kaplan-Meier analysis. Patients who died due to a cause not related to the OII or who underwent a planned removal of their implant in case of FRI and SII, were censored at the time of this event. SAT dosing and other factors potentially associated with failure were assessed by Cox proportional hazards models. Variables were considered for multivariable analysis in case of $p < 0.10$ in univariable analysis. SPSS Statistics for Windows was used (IBM SPSS Statistics for Windows, Version 29.0.0.0, Armonk, NY).

Results

During the study period, 113 patients were eligible for inclusion. Five patients were excluded: two patients were lost to follow-up within one month, two patients died within two weeks after initiation of SAT because of metastasized cancer, and in one patient PJI was unlikely based on the EBJIS 2021 criteria. The baseline characteristics of all 108 included patients are presented in Table 2.

Table 2 Baseline clinical characteristics of all 108 patients with suppressive antimicrobial therapy.

	All patients n = 108	Low dosage SAT n = 82	Standard dosage SAT n = 26
Age at diagnosis (median, IQR)	65 (50–73)	65.5 (50.8–74)	65.5 (36.3–72.3)
Male sex (n, %)	60 (56)	44 (54)	16 (62)
Comorbidities			
Smoker	23 (21)	18 (22)	5 (19)
BMI (mean, 95% CI)	26.5 (19–36.6)	26.5 (11.8–41.6)	26.8 (12.9–40.7)
Charlson comorbidity index (median, IQR)	3 (2–5)	3 (2–5)	3 (2–5)
Rheumatoid arthritis	9 (8)	7 (9)	2 (8)
Sarcoma	28 (26)	16 (20)	12 (46)
Chemotherapy	8 (7)	7 (9)	1 (4)
Type of implant			
Prosthetic joint	67 (62)	47 (57)	20 (77)
Tumor endoprosthesis[a]	38 (35)	25 (31)	13 (50)
Osteosynthesis	24 (22)	19 (23)	5 (19)
Spinal implant	17 (16)	16 (20)	1 (4)
Implant site			
Hip	35 (32)	23 (28)	12 (46)
Knee	29 (27)	22 (27)	7 (27)
Upper limb	13 (14)	11 (13)	2 (8)
Revised implant	43 (40)	33 (40)	10 (39)
Previous OII in the same joint	37 (34)	30 (37)	7 (27)
EBJIS 2021 criteria[b]			
Confirmed infection	86 (79)	62 (76)	24 (92)
Suggestive/likely infection	22 (17)	20 (24)	2 (8)
Timing infection			
Early postoperative	57 (53)	41 (50)	16 (62)
Acute hematogenous	13 (12)	10 (12)	3 (12)
Late chronic	38 (35)	31 (38)	7 (27)
C-reactive protein at diagnosis in mg/L (median, IQR)	76 (30–172)	73 (29–194)	103 (41–141)
C-reactive protein in mg/L at start SAT	10 (5–21)	10 (5–22)	9 (3–20)
Weeks of antibiotic treatment before SAT (median, IQR)	8 (6–13)	8 (6–13.3)	9 (6.8–13.3)
Indication for SAT			
Certain failure[c]	55 (51)	43 (52)	12 (46)
High risk of failure[d]	53 (49)	39 (48)	14 (54)

Table 2 Baseline clinical characteristics of all 108 patients with suppressive antimicrobial therapy. *(Continued)*

	All patients n = 108	Low dosage SAT n = 82	Standard dosage SAT n = 26
Microorganisms			
Staphylococcus aureus	35 (32)	29 (35)	6 (23)
Coagulase Negative Staphylococci	34 (32)	29 (35)	5 (19)
Gram-negatives	26 (24)	15 (18)	11 (42)
Enterococci	23 (21)	14 (17)	9 (35)
Streptococci	19 (18)	15 (18)	4 (15)
Cutibacterium acnes[e]	14 (14)	12 (15)	2 (8)
Anaerobes	10 (9)	9 (11)	1 (4)
Candida albicans	3 (3)	1 (1)	2 (8)
Corynebacteriae	3 (3)	3 (4)	0
Polymicrobial infection	42 (39)	30 (37)	12 (46)

The abbreviations used in the table are as follows: SAT - suppressive antimicrobial therapy; OII - orthopedic implant infection; CI – confidence interval; IQR – interquartile range. [a] subgroup of prosthetic joint. [b] according to EBJIS 2021 criteria for PJI and the AO Foundation and EBJIS 2020 consensus definition for FRI. [c] OII treated without any surgery, late chronic infection treated with DAIR or acute infection with failure of DAIR. [d] early postoperative and acute hematogenous OII treated with DAIR in the presence of risk factors for relapse. [e] formerly named *Propionibacterium acnes*.

Indications for SAT in patients with an acute PJI treated with DAIR (n = 27) were the presence of a tumor endoprosthesis (n = 18, 67 %), microorganisms associated with higher risk of relapse (n = 14, 52 %), comorbidity (n = 9, 33 %) or previous PJI treatment failures (n = 9, 33 %). Reasons for not performing any surgery in 19 patients were comorbidity (n = 10, 53 %) (metastasized cancer, chemotherapy and short life expectancy, COPD, heart failure), surgery related factors (n = 6, 16 %) (poor bone stock, soft tissue problems, prosthesis too complex to remove, non-consolidation of fracture, risks surgery disproportionate to the symptoms) or refusal by the patient (n = 6, 30 %). The diagnostic criteria for the patients who did not receive any surgery are summarized in Table S1.

The number of antibiotics that were used in this study are summarized in Fig. 1. More details regarding the dosing schedules are provided in Table S2.

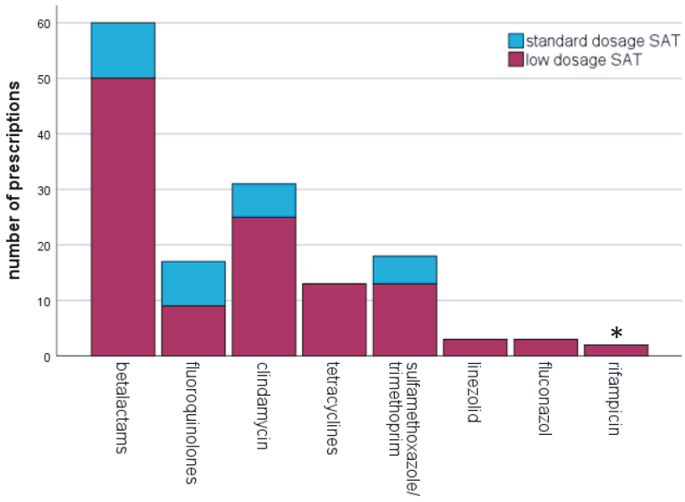

Figure 1 *Frequency of antibiotic use for oral suppressive antimicrobial therapy (SAT). * in combination with levofloxacin.*

Clinical outcomes

SAT was considered successful in 74/108 patients (69 %) with a median follow-up of 21.2 months (IQR 10.4–41.8 months). The success rate for patients with PJI, FRI and SII was 60 %, 88 % and 79 % respectively. The SAT failure-free survival in the low dosage group was lower compared to the standard dosage group, but this difference was not statistically significant (p = 0.63) (Fig. 2a). This outcome did not change when including only patients with PJI (Fig. 2b) or only patients from the group that had an indication for SAT because of "certain" relapse (if SAT be withheld) (Fig. 2c).

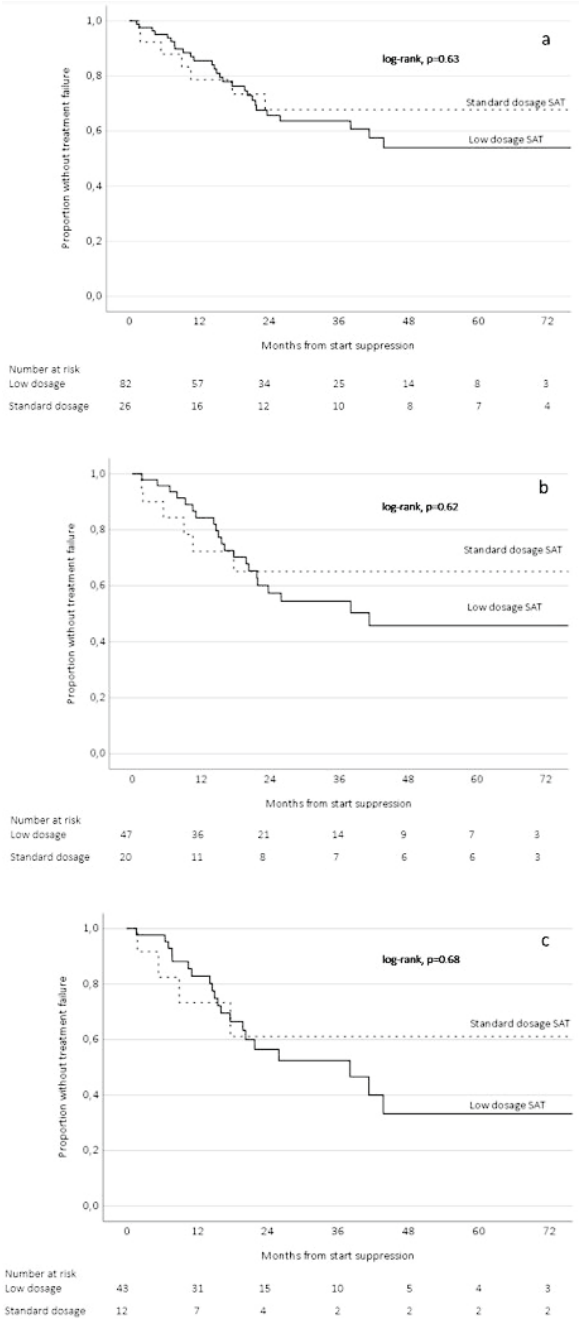

Figure 2 *Survival analysis related to low dosage and standard dosage SAT (a) including all orthopedic implant infections, (b) including only prosthetic joint infections, and (c) including only orthopedic implant infections with an indication for SAT because of "certain" relapse*

SAT was discontinued in 25 patients after a median time of 26.4 months (IQR 14.3–38.1 months). This group consisted of 12 PJI (48 %), nine FRI (36 %) and four SII (15 %). Eighteen of these patients (72 %) had a confirmed infection at the time of diagnosis. Five patients (20 %) did not undergo any form of surgery. The median C-reactive protein at start SAT was 8 mg/L (IQR 3–13 mg/L). SAT was stopped because of good clinical performance in 23 patients (92 %) and requested by the patient due to side-effects in two cases (8 %). The median follow-up duration of this group after discontinuation of SAT was 21 months (IQR 9.4–34.6 months). During this period, one patient with PJI (4 %) developed a culture-negative relapse. This occurred within one week after stopping SAT which the patient had received for 38 months. Of the 83 patients still on SAT at the end of the study, 23 patients had a follow-up beyond two years, of which two patients (9 %) had a relapse (after 41 and 44 months).

The details of the 34 patients with failure are summarized in Table 3. The median time to failure was 11.1 months (IQR 6.5–19.8 months). An overview of the cultured microorganisms in failed cases and details of the development of antimicrobial resistance is summarized in tables S3, S4 and S5. Fifteen of 108 patients (14 %) died due to non-OII related causes.

Table 3 Characteristics of all patients with failure treated with suppressive antimicrobial therapy.

	All patients n = 34	**Low dosage SAT n = 27**	**Standard dosage SAT n = 7**
Clinical outcome			
New surgery of infected joint, n (%)	18 (53)	12 (44)	6 (86)
Admission for iv antibiotics	3 (9)	3 (11)	0
Uncontrolled symptoms	4 (12)	3 (11)	1 (17)
Fistula	6 (18)	6 (22)	0
Increasing SAT to standard dosage	2 (6)	2 (7)	0
Relapse after stopping SAT	1 (3)	1(4)	0
Microbiological finding at time of failure			
Relapse with index pathogen	11 (32)	8 (30)	3 (43)
Development of SAT resistance	4 (12)	4 (15)	0
New infection with different pathogen	9 (26)	8 (30)	1 (14)
Culture negative	7 (21)	5 (19)	2 (29)
No tissue for cultures obtained	7 (21)	6 (22)	1 (14)

The abbreviations used in the table are as follows: SAT - suppressive antimicrobial therapy

Table 4 Analysis of clinical characteristics potentially associated with failure of suppressive antimicrobial therapy for all 108 patients

	Failure n (%)	Univariable analysis HR (95% CI)	p-value	Multivariable analysis aHR (95% CI)	p-value
Patient factors					
Age >70	14 (40)	1.33 (0.67–2.64)	0.41		
Smoker	9 (39)	1.92 (0.89–4.12)	0.10		
Charlson comorbidity index >2	24 (36)	1.33 (0.63–2.78)	0.46		
Diabetes mellitus	5 (56)	3.89 (1.48–10.2)	0.01		
Implant					
Prosthetic joint	27 (40)	1[a]			
Fracture related	5 (21)	0.53 (0.20–1.36)	0.19		
Spinal implant	2 (12)	0.32 (0.08–1.35)	0.12		
Previous implant infection	17 (46)	1.79 (0.91–3.51)	0.09		
Revised implant	21 (49)	2.17 (1.09–4.33)	0.03	2.10 (0.74–3.41)	0.23
Chronic OII	22 (42)	1.93 (0.96–3.9)	0.07		
Tumor endoprosthesis	15 (40)	1.40 (0.71–2.76)	0.33		
Anatomic location					
Hip	9 (26)	1[a]			
Knee	13 (45)	2.13 (0.91–4.99)	0.08		
Upper limb	7 (54)	3.17 (1.16–8.63)	0.02	2.10 (0.90–4.91)	0.09
Microbiology					
Staphylococcus aureus	8 (23)	0.76 (0.34–1.66)	0.47		
Coagulase negative staphylococci	14 (41)	1.59 (0.8–3.15)	0.19		
Streptococci	3 (16)	0.33 (0.1–1.09)	0.07		
Enterococci	8 (35)	1.21 (0.55–2.68)	0.64		
Gram-negatives	12 (46)	1.22 (0.58–2.56)	0.62		
Polymicrobial infection	13 (31)	1.03 (0.52–2.06)	0.93		
Clinical aspects					
<12weeks antibiotic treatment before SAT	23 (30)	0.79 (0.40–1.58)	0.51		
C-Reactive protein at start SAT >=20	10 (37)	1.83 (0.86–3.85)	0.12		
Low dosage SAT	27 (33)	1.23 (0.53–2.83)	0.63	1.12 (0.48–2.64)	0.79
No surgery performed	9 (47)	1.74 (0.81–3.73)	0.16		
Indication SAT Certain relapse	24 (44)	2.27 (1.29–5.72)	0.01	2.04 (0.89–4.70)	0.09

The abbreviations used in the table are as follows: HR – hazard ratio; CI – confidence interval; SAT – suppressive antimicrobial therapy. [a] Reference

Upper limb OII, diabetes mellitus, OII of a revised implant, and "certain" relapse group were associated with failure in the univariable but not in the multivariable analysis (Table 4). After selecting only patients with PJI in the analysis, upper limb PJI (HR 4.41, 95 % CI 1.41–13.76) and diabetes mellitus (HR 3.95, 95 % CI 1.43–10.92) were independently associated with failure (Table S6).

Reported side effects

Of 147 prescriptions, side effects were reported 36 times (24 %) by 31 individual patients (30 %). This led to a switch of antibiotic treatment 18 times in 12 patients (12 %) and cessation of antibiotics in two patients (2 %). Gastro-intestinal side effects were most frequently reported (26/36, 72 %), followed by rash (5/36, 14 %), hepatitis (2/36, 6 %), renal failure (1/36, 3 %), tendinitis (1/36, 3 %) and oral candidiasis (1/36, 3 %). The frequency of side effects was not different between patients on low dosage SAT and those on standard dosage SAT (p = 0.82). Detailed characteristics of the reported side effects per antimicrobial regimen are summarized in Table S7.

Discussion

In this cohort study, patients with OII treated with low dosage SAT had a comparable outcome as patients treated with the standard dosage of antibiotics. The overall SAT success rate of 69 % is in line with comparable studies on SAT in OII that reported success rates between 59 % and 72 % (Prendki et al., 2017; Pradier et al., 2018; Escudero-Sanchez et al., 2020). To the best of our knowledge, this is the first study in OII focusing on the effectiveness of low dosage SAT. Several studies on PJI included patients on lower dosed SAT but did not compare its effectiveness with standard dosage SAT (Siqueira et al., 2015; Bryan et al., 2017; Prendki et al., 2017; Wouthuyzen-Bakker et al., 2017; Leijtens et al., 2019).

Patients with OII on SAT represent a heterogenous group with a prognosis that is dependent on the timing of infection, the initial treatment and host factors. For the patients who were categorized in the "certain" relapse (if SAT would have been withheld) group, we deemed it very unlikely that the infection was cured after initial treatment (i.e., patients treated with antibiotics only, late chronic infections treated with DAIR, and patients with a failure after the initial DAIR). In the "high-risk" group of patients, the risk of a relapse was considered to be substantial (if SAT would be withheld) but not as high as in the "certain" group. The success rate of the "high risk" group (81 %) was indeed higher than the "certain" group (56 %). It cannot be excluded that a proportion of patients within the "high risk" group may have received

SAT while their infection was already cured. This is a well-known uncertainty for all physicians who consider SAT for their patients with OII. Nonetheless, the outcomes of the survival analyses in this study suggest that low dosage antibiotics could be a viable option for all patients on SAT, including patients whose infection will almost certain relapse without suppression (Fig. 2c).

Duration of SAT

In many studies SAT is recommended to be prescribed 'indefinitely' (Marculescu et al., 2006; Byren et al., 2009; Prendki et al., 2017; Escudero-Sanchez et al., 2020). This is likely due to the uncertainty whether chronic OII can ever be cured without implant removal and if so, in which patients and within what timeframe. Ideally, the duration of antibiotic treatment is based on the lifespan of the bacteria in the biofilm but this lifespan is currently unknown. In our study, stopping SAT after two to three years resulted in a very low relapse rate, comparable to continuing SAT beyond two years. Moreover, 19 patients in our study were treated with antibiotics only (i.e., no surgical debridement or implant removal) and in five of those patients the discontinuation of SAT did not result in a relapse during 12 months follow up. Our observation that curation of OII may be achieved after a certain period of SAT has been reported before. Pavoni et al (n = 29) reported a cure rate of 66 % after stopping SAT within one year, but the indication for initiating SAT was not clearly defined in this paper (Pavoni et al., 2004). No relapses were reported by Bene et al in 24 patients with acute PJI of the knee who stopped SAT after 20 months and a follow-up of four years (Bene et al., 2018). Pradier et al reported 15 failures in 52 patients (29 %) on indefinite SAT compared to two relapses in 26 patients (8 %) in a historical cohort with a maximal duration of two years of SAT. Five other observational studies with a combined total of 120 patients reported sporadic SAT cessation after six to 36 months in 15 patients with one subsequent relapse (7 %) (Goulet et al., 1988; Segreti et al., 1998; Rao et al., 2003; Leijtens et al., 2019; Sandiford et al., 2019). Byren et al (n = 112) found a fourfold increase in relapse in the first four months after stopping SAT after a median time of 15 months in patients with PJI treated with DAIR, but this occurred only in a minority of patients and most of the patients were actually cured (Byren et al., 2009). In the study of Shah et al (n = 108), which included patients with knee PJI managed by DAIR, extending SAT beyond 12 months did not result in better outcome (Shah et al., 2020).

The majority of relapses in our cohort occurred in the first two years during treatment with SAT which is consistent with other studies (Prendki et al., 2017; Weston et al., 2018; Leijtens et al., 2019; Escudero-Sanchez et al., 2020). The relapse rate in the group of patient on SAT beyond two years was only 9 % in our study. In the largest cohort on SAT in PJI published to date (n = 302), 33 % of failures was a microbiologi-

cally confirmed relapse and only 17 % of relapses could be attributed to the cessation of SAT (Escudero-Sanchez et al., 2020). The discrepancy in causative microorganisms between the initial OII and the subsequent relapse raises the question whether most late failures on SAT actually stem from new infections with microorganisms that SAT could not have prevented. Further, a substantial part of SAT failures were culture negative. This suggests that the infection was cured but SAT could not prevent loosening of the implant.

In short, the assumption that every patient with OII and an indication for SAT needs to be treated indefinitely can be challenged: Some patients might have been cured already before initiation of SAT and for a subgroup of patients with an apparent "incurable" infection, two to three years of treatment with SAT (or perhaps even shorter) seems sufficient in case of a favorable clinical course. To reliably assess and decide in whom and when SAT can safely be stopped, it is essential to use a personalized approach for each individual patient on suppression.

Concept of SAT

SAT is usually preceded by surgical debridement and a therapeutic antimicrobial phase with the goal to eradicate all metabolically active bacteria in the soft tissue, surrounding bone and biofilm. For this goal, dosing is based on pharmacokinetic and pharmacodynamic (PK/PD) indices for optimal effectiveness (Onufrak et al., 2016). After this phase, eventual remaining biofilm still contains metabolically inactive, dormant bacteria, so called persisters, against which antibiotics are not effective (Mcconoughey et al., 2014). The only purpose of SAT is to kill those bacteria that switch back from a dormant state to metabolically active bacteria capable of causing a relapse of the infection. Within this concept it is probable that the PK/PD targets for SAT are lower than for therapeutic treatment and the results of this study with lower dosed antibiotics support this hypothesis. Some patients with chronic OII were cured without implant removal. This suggests that degradation of the biofilm matrix on these implants and/or eradication of all bacteria including persisters can occur during SAT. This conceptual model of SAT is illustrated in Figure 3.

Currently, the exact pathophysiology and duration of such a degradation process are unknown and data on biofilm durability in OII while being treated with long-term antibiotics are absent. More insight in the pathophysiology of biofilms is needed to relate the strategy of stopping SAT after a set amount of time as well as lower (or less frequently) dosing of SAT to treatment success.

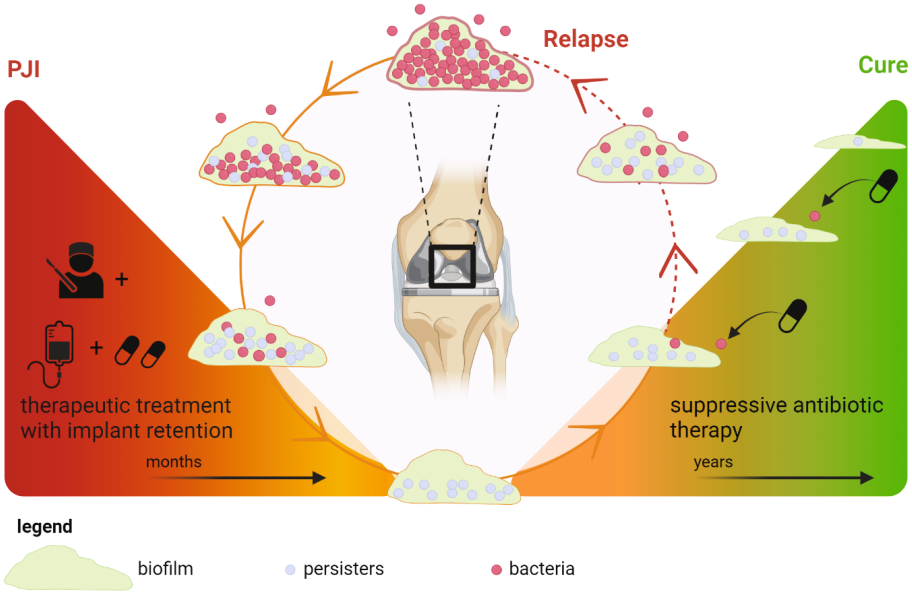

Figure 3 *Concept of biofilm development during suppressive antimicrobial treatment in prosthetic joint infection.*
Left triangle: Treatment of a chronic prosthetic joint infection with debridement and implant retention followed by therapeutic antimicrobial treatment. During this phase all metabolically active bacteria in the (peri-)prosthetic tissue are killed but some persisters endure in the biofilm. Right triangle: Suppressive antimicrobial therapy (SAT) is only aimed at those bacteria that switch back from a persister state to a metabolically active state, thereby preventing spread into the periprosthetic tissue which otherwise would lead to clinical relapse. For this specific goal, low dosage SAT could be sufficient. Under these conditions the biofilm slowly degrades and cure can be achieved.
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Suppressive treatment for FRI and SII

This cohort contains the largest group of FRI treated with SAT to date. Only one small observational study reported on SAT for patients with FRI (n = 5) (Ceccarelli et al., 2023). Data on SAT in SII are also scarce with the largest cohort reporting a two year survival free of treatment failure of 71 % in acute SII treated with DAIR followed by SAT compared to 33% in those with acute SII treated with DAIR without SAT (Kowalski et al., 2007). The failure rate in our study was 21 % for SII. Although not statistically significant (likely due to the small sample size), PJI was associated more strongly with failure than FRI and SII. Although the pathophysiological concept of biofilm (formation) and treatment is the same for all OII, differences in local anatomy, condition of soft tissue, type of bone and foreign body material might influence clinical

outcomes. More data are needed to understand the similarities and differences of these infections.

Antibiotics used

Beta-lactams and clindamycin were the most commonly used antibiotics in this study. Effectiveness and side effects were similar for the different antibiotics used in this study and consistent with other research (Siqueira et al., 2015; Leijtens et al., 2019; Escudero-Sanchez et al., 2020). Lower dosing did not result in less side effects. Perhaps even lower dosages are needed to reduce toxicity of these drugs. When choosing a drug for chronic antimicrobial therapy, side effects, drug-drug interactions and dosing frequency should be taken into account. Once daily regimens may improve medication adherence but this has not been studied in SAT (Coleman et al., 2012; Weeda et al., 2016). Expert opinion-based dosing schedules for SAT in OII from our institution are provided in Table 5.

Table 5 Expert opinion-based dosing schedules for suppressive antimicrobial therapy in orthopedic implant infections.

Drug	Dosing
Amoxicillin	500 mg b.i.d.
Flucloxacillin	1000 mg b.i.d.
Amoxicillin/clavulanic avid	625 mg b.i.d.
Ciprofloxacin and levofloxacin	500 mg q.d.
Clindamycin	600 mg b.i.d.
Trimethoprim/sulfamethoxazole	960 mg q.d.
Tetracyclines	100 mg q.d.
Linezolid	300 mg q.d.

The abbreviations used in the table are as follows: q.d. - once daily; b.i.d. - twice daily.

Strengths and limitations

This study evaluated the effectiveness and side effects of well-specified different antimicrobial dosing strategies for SAT. Furthermore, this study included the largest series of patients with FRI treated with SAT. By including patients with a relatively short minimum follow-up duration, we reduced the possibility of missing early failures.

The study has several limitations, e.g. due to its retrospective design, selection bias and confounding cannot be fully excluded. Adverse effects were not documented in a uniform manner. The study population is heterogenous regarding outcome because SII an FRI might have better prognosis than PJI. The relatively limited size of our cohort necessitates prospective data to validate these results. Lastly and most

importantly, confirmative parameters which can discern cured patients from patients with a persistent biofilm, do not exist. This likely has resulted in patients receiving SAT while the infection was already cured after initial management as discussed above.

Conclusions

Based on this study, lower and/or less frequently dosed antibiotics may be a safe treatment option for patients with OII who have an indication for chronic suppressive therapy. Furthermore, stopping SAT after two to three years may be justified in patients who are clinically stable. This decision needs to be weighed for each individual patient. More research is needed to evaluate which patients really need SAT after the initial treatment phase. Further, larger cohort studies are warranted to confirm and validate the findings of this study, to determine optimal dosing and duration of SAT and to identify an optimal set of clinical criteria for safe discontinuation.

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Supplement

Table S1 diagnostic criteria of the 19 patients that did not receive surgery for the orthopedic implant infection.

Infection	Diagnosis[a]	Diagnostic criteria[a]	Microorganism
FRI upper arm	confirmed	Fistula, positive culture from aspiration	*Cutibacterium acnes*
PJI hip	likely	fever, wound healing history, CRP >10mg/l, positive culture from aspiration	*Streptococcus agalactiae*
PJI hip	likely	fever, wound healing history, CRP >10mg/l, positive culture from aspiration	*Staphylococcus epidermidis*
PJI hip	likely	Fever, purulence prosthesis, CRP >10mg, positive culture from aspiration	Group B *Streptococci*
FRI leg	confirmed	Fistula, positive culture from aspiration,	*Cutibacterium acnes*
PJI knee	likely	Radiological loosening, CRP >10mg/ml, positive culture from aspiration	*Staphylococcus haemolyticus*
FRI pelvis	suggestive	Bacteremia, fever, pain, PET suggestive of infection	*Staphylococcus aureus*
PJI shoulder	likely	Fever, pain, CRP>10mg/L, PET suggestive of infection, positive culture from aspiration	*Cutibacterium C. acnes*
PJI hip	likely	Fever, pain, CRP>10mg/L, ultrasound suggestive of infection, positive culture from aspiration	*Staphylococcus aureus*
PJI hip	likely	Fever, pain, CRP>10mg/L, ultrasound suggestive of infection, positive culture from aspiration	*Staphylococcus aureus*
FRI elbow	suggestive	Pain, redness, CRP>10mg/L, ultrasound suggestive of infection, positive culture from aspiration	*Staphylococcus epidermidis*
SII	suggestive	Pain, fever, CRP>10mg/L, CT suggestive of infection, positive culture from CT guided aspiration	*Staphylococcus aureus*
PJI knee	suggestive	Fever, pain, redness, previous wound healing problems CRP>10mg/L, positive culture from aspiration	*Staphylococcus aureus*
PJI hip	confirmed	>2 intraoperative cultures	*Staphylococcus haemolyticus*
PJI knee	suggestive	Recent bacteremia, fever, redness, CRP>10mg/L, positive culture from aspiration	*Streptococcus oralis*
PJI shoulder	suggestive	Redness, radiological signs of loosening, CRP>10mg/L, positive culture from aspiration	*Cutibacterium acnes*
PJI shoulder	suggestive	Fever, redness, CRP>10mg/L, positive culture from aspiration (pus)	*Cutibacterium acnes*
PJI elbow	confirmed	Fistula, positive culture from aspiration	*Enterobacter cloacae*
PJI knee	suggestive	Redness, pain, radiological loosening, ultrasound suggestive of infection, positive culture from aspiration (pus)	*Staphylococcus epidermidis*

The abbreviations used in the table are as follows: FRI – fracture related infection; PJI - prosthetic joint infection; SII – spinal implant infection. [a]according to EBJIS 2021 criteria for PJI and the AO Foundation and EBJIS 2020 consensus definition for FRI.

Table S2 Characteristics of the antibiotic prescribed for suppressive antimicrobial treatment (SAT) in 108 patients with an orthopaedic implant infection

Antibiotic	Number of prescriptions (n, %)	Daily dosage (n)	Duration SAT in month mean (range)	Failure (n, %)
Flucloxacillin	26	1000 mg q.i.d. (3)	11 (1-91)	7 (27)
		1000 mg t.i.d. (3)		
		1000 mg b.i.d. (12)		
		500 mg q.i.d. (1)		
		500 mg t.i.d. (1)		
		500 mg b.i.d. (6)		
Amoxicillin	25	1000 mg q.i.d. (3)	18 (1-81)	3 (12)
		1000 mg t.i.d. (1)		
		1000 mg b.i.d. (10)		
		500 mg q.i.d. (2)		
		500 mg t.i.d. (1)		
		500 mg b.i.d. (7)		
		750 mg b.i.d. (1)		
Amoxicillin/clavulanic acid	6	1250 mg t.i.d. (1)	7 (1-26)	2 (33)
		1250 mg b.i.d. (1)		
		625 mg b.i.d. (4)		
Feneticillin	3	500 mg q.i.d. (2)	32 (20-41)	2 (66)
		500 mg b.i.d. (1)		
Clindamycin	31	600 mg t.i.d. (3)	18 (1-117)	7 (22)
		600 mg b.i.d. (20)		
		300 mg b.i.d. (5)		
		300 mg t.i.d. (4)		
Sulfamethoxazole/ trimethoprim	18	960 mg b.i.d. (5)	16 (4-62)	4 (22)
		960 mg q.d. (11)		
		480 mg q.d. (2)		
Doxycycline	14	100 mg q.d. (14)	23 (5-62)	2 (14)
Ciprofloxacin	9	750 mg b.i.d. (4)	23 (1-69)	3 (30)
		500 mg b.i.d. (1)		
		750 mg q.d. (3)		
		500 mg q.d. (1)		
Levofloxacin	5	500 mg q.d. (4)	22 (1-33)	1 (20)
		250mg q.d. (1)		
Moxifloxacin	3	400 mg q.d. (3)	10 (4-92)	0
Linezolid	3	600 mg q.d. (1)	11 (9-33)	1 (33)
		300 mg q.d. (1)		
		150 mg q.d. (1)		
Rifampicin	2	300 mg q.d. (2)	21-22	1 (50)
Fluconazole	3	200 mg q.d. (3)	17 (1-117)	1 (33)

The abbreviations used in the table are as follows: q.d. - once daily; b.i.d. - twice daily; t.i.d. - three times a day; q.i.d. - four times a day.

Table S3 Microbiological characteristics of the index pathogens of the 34 patients with failure on suppressive antimicrobial treatment (SAT)

	All failures (%)	Relapse with index pathogen	Development of SAT resistance	New infection with different pathogen	Culture negative	No tissue for cultures obtained
Number of patients (%)	**34 (100)**	**11 (32)**	**4 (12)**	**9 (26)**	**7 (21)**	**7 (21)**
Index pathogen						
Staphylococcus aureus	8 (24)	2	1	3	1	2
Coagulase negative staphylococci	14 (41)	4	2	4	4	2
S. epidermidis	11	4	2	3	3	1
S. hemolyticus	2			1		1
S. capitis	1				1	
Gram negative species	12 (35)	4		5	2	1
Pseudomonas aeruginosa	4 (9)	1		2	1	
E. coli	1			1		1
Acinetobacter baumanii	1	2		1	1	
Proteus mirabilis	3	1				
Enterobacter cloacae	3			1		
Enterococci	8 (24)	2		3	2	1
E. faecalis	6	1		3	1	1
E. faecium	2	1			1	
Streptococci	3 (9)	1	0		2	
S. agalactiae	1				1	
Beta-hemolytic streptococci	2	1			1	
Cutibacterium acnes	5 (6)	1	1		1	2
Candida albicans	2 (6)			1	1	
Bacteroides fragilis	1 (3)	1				
Corynebacterium species	1 (3)			1		
Polymicrobial	13 (38)	3		4	5	1

Table S4 Microbiological characteristics of the 9 patients with failure with a new pathogen cultured

Index pathogen(s)	New pathogens(s)
Staphylococcus aureus, Pseudomonas aeruginosa, Enterococcus faecalis	*Stenotrophomonas maltophilia, Achromobacter xylosoxidans, Enterococcus faecium, Candida albicans*
Staphylococcus haemolyticus, Pseudomonas aeruginosa, Enterococcus faecalis	*Staphylococcus epidermidis*
Staphylococcus epidermidis	*Staphylococcus epidermidis*, Peptoniphilus species, *Prevotella melaninogenica*
Staphylococcus aureus	*Enterococcus faecalis*, alpha hemolytic streptococci
Staphylococcus epidermidis, Enterococcus faecalis, Escherichia coli	*Morganelli morgani, Bacteroides fragilis, Pseudomonas aeruginosa, Staphylococcus epidermidis*
Staphylococcus aureus	*Enterococcus faecalis, Escherichia coli, Klebsiella pneumoniae, Proteus vulgaris*
Candida albicans	*Enterococcus faecalis, Staphylococcus aureus*
Staphylococcus epidermidis, Acinetobacter baumanii, Corynebacterium species	Anaerococcus species
Enterobacter cloacae	*Streptococcus agalactiae*

Table S5 Time to failure in 4 patients with development of resistance against suppressive antimicrobial treatment

Index pathogen	Antibiotic treatment	months of treatment till relapse
Staphylococcus aureus[a]	flucloxacillin 1000 mg b.i.d.	15
Staphylococcus epidermidis	doxycycline 100 mg q.d.	9
Staphylococcus epidermidis	flucloxacillin 500 mg t.i.d.	11
Cutibacterium acnes	clindamycin 300 mg b.i.d.	22

[a] cultures of relapse showed a borderline resistant *Staphylococcus aureus* (BORSA) with a MIC for oxacillin of 6 mg/L.

Table S6 Analysis of clinical characteristics potentially associated with failure of suppressive antimicrobial therapy for patient with PJI (n=67)

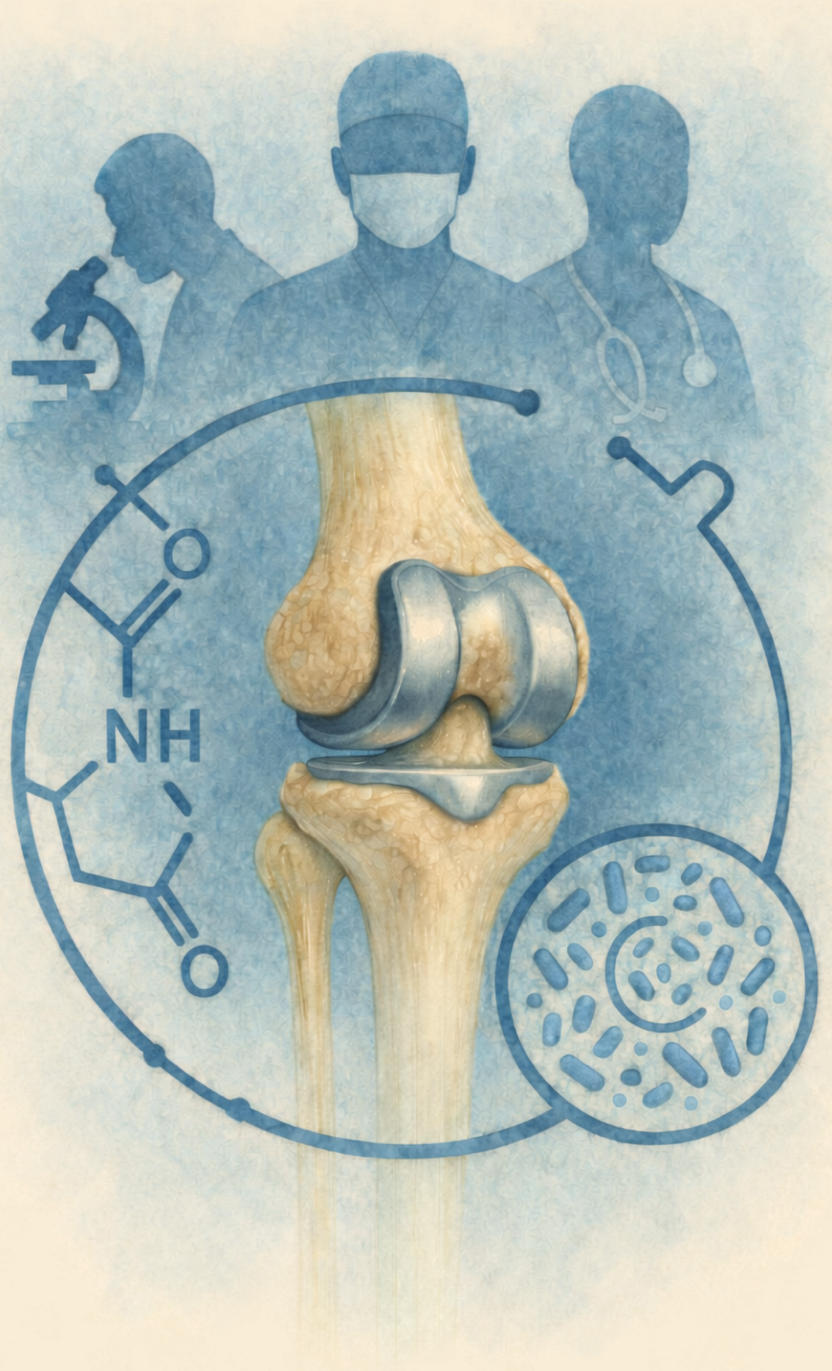
	Failure n (%)	Univariable analysis HR (95% CI)	p-value	Multivariable analysis HR (95% CI)	p-value
Patient factors					
Age >70	13 (43)	1.31 (0.61–2.79)	0.49		
Smoker	5 (50)	2.06 (0.77–5.51)	0.15		
Charlson comorbidity index >2	19 (37)	0.67 (0.29–1.55)	0.35		
Diabetes mellitus	4 (67)	4.08 (1.38–12.052)	0.01	4.41 (1.41–13.76)	0.01
Previous PJI	16 (49)	1.34 (0.62–2.89)	0.45		
Revised prosthesis	18 (51)	1.47 (0.66–3.27)	0.35		
Chronic PJI	18 (46)	1.46 (0.66–3.25)	0.35		
Tumor endoprosthesis	15 (40)	0.99 (0.46–2.11)	0.97		
Anatomic location					
Hip	8 (25)	1			
Knee	13 (48)	2.29 (0.95–5.54)	0.07		
Upper limb	6 (75)	6.21 (2.07–18.59)	0.01	3.95 (1.43–10.92)	0.01
Microbiology					
Staphylococcus aureus	5 (33)	0.86 (0.32–2.27)	0.76		
Coagulase negative staphylococci	11 (44)	1.13 (0.52–2.44)	0.76		
Streptococci	3 (20)	0.29 (0.09–0.98)	0.05	0.42 (0.12–1.45)	0.17
Enterococci	5 (39)	1.12 (0.42–2.95)	0.82		
Gram-negatives	6 (50)	1.33 (0.54–3.31)	0.54		
Polymicrobial infection	13 (31)	1.03 (0.46–2.31)	0.93		
Clinical aspects					
<12weeks antibiotic treatment before SAT	17 (40)	1.12 (0.51–2.42)	0.80		
C-Reactive protein at start SAT >=20	10 (46)	1.87 (0.82–4.30)	0.14		
Low dosage SAT	21 (45)	1.26 (0.51–3.13)	0.62	1.05 (0.41–2.69)	0.92
No surgery performed	7 (50)	1.45 (0.61–3.45)	0.40		
Indication SAT "certain failure"	21 (48)	2.10 (0.84–5.25)	0.11	1.89 (0.71–5.02)	1.89

The abbreviations used in the table are as follows: HR – hazard ratio; CI – confidence interval; SAT – suppressive antimicrobial therapy. [a] Reference

Table S7 Reported side effects of suppressive antimicrobial treatment per antibiotic

Antibiotic	Side effects (n)	Switch or stop SAT (n, %)
Flucloxacillin	GI (4)	4 (15)
Amoxicillin	GI (8)	3 (12)
	skin (1)	
Amoxicillin/clavulanic acid	GI (1)	0
	oral candida (1)	
Feneticillin	GI (2)	
Clindamycin	GI (9)	7 (22)
	skin (1)	
	liver (1)	
Sulfamethoxazole/trimethoprim	GI (1)	1 (6)
	Renal (1)	
Doxycycline	Skin (2)	2 (14)
Ciprofloxacin		0
Levofloxacin	Liver (1)	2 (40)
	Tendon (1)	
Moxifloxacin		0
Linezolid	Skin (1)	1 (33)
	GI (1)	
Rifampicin		0
Fluconazole	GI (1)	0

The abbreviations used in the table are as follows: SAT - suppressive antimicrobial treatment; GI - gastrointestinal.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Chapter 8

Summary and general discussion

Summary and general discussion

Prosthetic joint infections (PJI) impose a significant burden on patients, physicians, and healthcare systems. Driven by factors such as an ageing population, comorbidities, polypharmacy, and rising antimicrobial resistance, the management of PJI has become increasingly demanding. These changes in patient characteristics and clinical complexity necessitate multidisciplinary collaboration to optimize care and individualize both surgical and antimicrobial strategies. Debridement, antibiotics, and implant retention (DAIR) has become an important treatment option for PJI, both as a curative strategy in acute infections and as a salvage or palliative approach when exchange arthroplasty is indicated but not feasible or acceptable. However, current clinical data to guide antimicrobial therapy in PJI treated with DAIR and curative intent are mainly derived from observational studies which limits causal inference when comparing the efficacy of different antimicrobial regimens. In addition, the role of long-term suppressive antimicrobial therapy (SAT) beyond the initial therapeutic antimicrobial treatment phase of PJI remains uncertain. Despite its common use, there is considerable worldwide variation in the clinical practice of SAT as a result of insufficient and low-quality evidence. Many clinical questions on SAT remain unresolved, and uniform definitions are scarce.

This thesis addresses several of these important aspects of antimicrobial treatment in patients with PJI, which are summarized and discussed here.

Part 1: Multidisciplinary care for complex bone and joint infections

In 2015, our hospital implemented a multidisciplinary team (MDT) to optimize care for patients with PJI and other complex bone and joint infections (BJI). The team comprises orthopedic surgeons, infectious diseases specialists, and clinical microbiologists; trauma surgeons, who initially joined occasionally, have become permanent participants over time. In **chapter 2**, we analyzed the effectiveness of our MDT meetings by evaluating the implementation rate of MDT decisions, a recognized proxy for effective multidisciplinary decision-making used in many medical fields, but not performed before in PJI (1). We assessed 1321 MDT decisions concerning 509 individual patients, made during 319 meetings. The overall decision implementation rate was high (92%), comparable to other medical specialties. This finding confirms our clinical experience that the MDT serves as an effective instrument capable of achieving a broadly supported consensus. Not implementing MDT surgical management decisions was associated with poor clinical outcomes—a novel yet unsurprising finding. Patient preference played a role here; in some cases, the MDT's surgical plan was not followed, patients refused surgery for reasons unknown to the MDT at the time of

the meeting during which the decision was made. Thus, an optimal surgical plan from the MDT's (i.e., doctor's) point of view is not necessarily the best treatment option from a patient's point of view. Although this seldom occurred it stresses the importance of shared decision making and tailoring treatment plans, especially concerning complex and disabling surgical treatments or burdensome antimicrobial therapies. To ensure that patient preferences are adequately represented during MDT discussions, potential strategies include involving patients directly in selected MDT meetings and appointing a dedicated nurse to explore and communicate their preferences.

Treating PJI and other BJI is complex and demands surgical, infectious diseases, and pharmacological expertise. Our study showed that such care benefits from structured cooperation between diverse medical specialists. The most effective form of collaboration involves a team-based approach that meets regularly to discuss all relevant cases and key diagnostic or therapeutic decisions throughout treatment (both during admission and outpatient). The team should consist of dedicated members from relevant specialties who ideally attend every meeting. The MDT aims to improve clinical outcomes relevant to patients through multiple benefits: better interdisciplinary understanding, lower consultation thresholds, standardized treatment and follow-up, increased member knowledge and expertise, and joint monitoring of complex cases (2-5). Other potential long-term advantages include cost reduction by decreasing hospital admission days, avoiding unnecessary surgical and diagnostic procedures, and reducing (broad-spectrum) antimicrobial consumption (6, 7).

Given these potential benefits, an MDT is widely recognized as a valuable component of PJI and complex BJI care (7-9). To establish a successful MDT, inspiring pioneers from the involved specialties are essential to motivate other physicians and organize the necessary infrastructure. However, such efforts require considerable time and resources. Implementation of MDTs should therefore be supported by data as much as possible to facilitate the deployment of MDTs and convince policy-makers and physicians alike (4). Current studies on PJI MDTs mainly report on the effect of the MDT on clinical parameters such as cure rates, length of hospital stay, and antimicrobial use, often showing improved outcomes post-implementation (6, 7, 10-14). Yet, to fully assess benefits of MDTs and to increase their effectiveness, future research should broadly evaluate all different aspects of multidisciplinary care, including guideline adherence, meeting attendance, documentation of decisions, patient involvement, and cost-effectiveness (1, 4).

Looking ahead, MDT-based PJI care could be improved by strengthening the incorporation of patient preferences and by more explicitly considering psychological and

social consequences of PJI (treatment)—either through direct patient participation in selected meetings or by appointing a dedicated PJI nurse to represent patient interests. Moreover, better structuring the communication of MDT decisions to patients could further improve understanding and acceptance of treatment plans. Artificial intelligence (AI)-based decision-support tools and AI-assisted case summaries are expected to help ensure that all relevant data are available in real time, enhance meeting efficiency, and support more consistent decision-making. Recent reviews have already explored the possibilities and limitations of AI in MDT care, orthopedics, infectious diseases, and PJI but specific studies on its application in team-based orthopedic infection care are not yet available (15-20). While technological advances may result in better MDT performance, future healthcare policy decisions will determine the role of multidisciplinary care within PJI management. In time, the presence of a well-functioning MDT may become a formal prerequisite for hospitals to provide this type of care, ensuring standardized and high-quality management. Until such standards are universally implemented, smaller hospitals without a local MDT should strive to participate through digital or regional MDT meetings, allowing complex cases to still benefit from multidisciplinary expertise.

To conclude, well-organized multidisciplinary care is critical for optimal and individualized treatment of patients with PJI. All clinicians involved in PJI management are encouraged to participate in or help establish multidisciplinary teams to increase inter-specialty engagement and collaboration aimed at providing the best possible care for patients.

Part 2: Antimicrobial Strategies for Debridement, Antibiotics, and Implant Retention

The second part of this thesis focuses on oral antimicrobial treatment strategies for PJI treated with DAIR. **Chapter 3** contains the protocol of the RIfampicin Combination Treatment versus Targeted oral Antimicrobial monotherapy for staphylococcal prosthetic joint infection (RICOTTA) trial. This is a multicenter randomized clinical trial (RCT) we are currently conducting in the Netherlands. We discuss methodological and practical aspects of the trial design to enhance patient recruitment, one of the major challenges in PJI clinical trials (21). The trial aims to confirm the hypothesis that monotherapy with clindamycin is non-inferior to rifampicin-based combination therapy during the targeted oral treatment phase of staphylococcal PJI treated with DAIR, thereby challenging recommendations from current guidelines (22, 23).

Although rifampicin-based combination therapy has long been recommended as the standard of care for staphylococcal implant-associated infections, this approach is based on limited clinical data. A critical appraisal of the available evidence made clear

that the foundation for this recommendation is remarkably weak and inconclusive. In the late 1990s, rifampicin-based therapy became first-line treatment for staphylococcal implant-associated infections, based on promising in vitro studies, animal cage models, and one RCT (n= 15 PJI) that seemed to confirm the preclinical findings (24). More recently, an RCT published in 2020 (n=48) and a prospective observational study (n=200) found no difference in outcomes between rifampicin-based regimens and monotherapy for staphylococcal PJI (25). Both RCTs were underpowered and hampered by methodological shortcomings, precluding any definitive recommendations regarding the necessity of rifampicin in this setting. This lack of clear evidence favoring rifampicin-based therapy, combined with high rates of drug discontinuation due to side effects and drug–drug interactions in rifampicin–fluoroquinolone combination therapy, provide the rationale for conducting the RiCOTTA trial (26).

In **chapter 4**, we analyzed data from 74 patients with Gram-negative (GN) PJI from our prospective multicenter clinical PJI registry. The study focused on the effectiveness of antimicrobial therapy in patients with newly placed or retained implants. This study suggests that there is no difference in outcome between patients treated with fluoroquinolones (FQ) and those treated with cotrimoxazole during the oral treatment phase of DAIR. Treatment with beta-lactams was associated with poorer outcomes, likely reflecting selection bias. The observational design and small sample size limit definitive conclusions and results must be interpreted alongside existing data.

Like rifampicin-based therapy for staphylococcal PJI, FQs are regarded as first-line for GN-PJI due to good bioavailability, excellent bone penetration, and promising preclinical biofilm experiments (27-30). Unfortunately, clinical studies—all retrospective observational cohorts—offer inconsistent evidence on whether FQs are more effective than other antibiotics for GN-PJI treated with DAIR (or 1SR) (31-38). No study compared FQ monotherapy head-to-head with other oral monotherapies and many patients received combination therapy, further complicating the interpretation of results. Given an increasing FQ resistance in GN infections, including PJI, alternative effective and safe oral regimens are urgently needed. Cotrimoxazole, the combination of sulfamethoxazole and trimethoprim, is a practical alternative because of its comparable bioavailability, bone and synovial fluid penetration, and activity against Gram-negative organisms (29). A few preclinical studies have investigated cotrimoxazole and shown less efficacy in GN biofilm infections when compared to FQs (30, 39). Clinical data about the use of cotrimoxazole for the treatment of GN-PJI are extremely scarce, with only four case series reporting a combined success rate of 69% in a total of 35 patients, most of whom received at least one other antimicrobial

drug targeting the GN pathogen. (33, 35, 37, 40). For both FQs and cotrimoxazole, adverse effects remain a concern.

Cotrimoxazole may cause, among others, cutaneous reactions, renal impairment, and bone marrow toxicity, while fluoroquinolones are associated with tendinopathy, QT prolongation, and peripheral neuropathy. Oral agents such as fosfomycin and beta-lactams lack supportive clinical data for managing GN-PJI, and their limited bioavailability and suboptimal bone penetration further raise concern for their utility.

Many observational retrospective studies have concluded that rifampicin-based therapy for staphylococcal PJI and FQ-based therapy for GN-PJI are associated with better outcome. Unfortunately, confounding by indication, immortal time bias and selection bias hampered the majority of these studies (41). Furthermore, head-to-head comparison of different well-defined strategies was rarely performed. Most studies compared all patients treated with rifampicin (or FQ) with all other treatment regimens combined (i.e., non-rifampicin group or non-FQ group) instead of a specific strategy (e.g., clindamycin monotherapy or cotrimoxazole monotherapy). Earlier work from our study group argued that this study design potentially introduces bias towards the better defined regimens and likely underestimates the effectiveness of specific strategies within the non-rifampicin or non-FQ group (42, 43). Such studies carry the risk of unsubstantiated exclusion of equally effective alternative treatments.

Altogether, clinical data on the superiority of current first-line treatment options for PJI treated with DAIR (i.e., rifampicin for staphylococcal PJI and fluoroquinolones for GN-PJI) remain contradictory and inconclusive. How can that be reconciled with the promising preclinical results of these antimicrobial drugs? Experimental animal cage models have demonstrated that rifampicin-FQ combination therapy can effectively eradicate staphylococcal implant associated infections with incubation periods of 2–3 days while monotherapy with FQ, vancomycin, daptomycin, or linezolid failed to do so (44). However, in similar studies where biofilm incubation was extended to 14 days, rifampicin-based therapy failed to cure any animals (45). This observation may partly explain the lack of clear benefit of these 'biofilm-active' agents in clinical studies, as biofilms encountered in patients with PJI are often at least 1-2 weeks old, making eradication by antibiotic therapy unlikely. Moreover, other factors are likely to contribute as well. These include fundamental differences in host immunology and local anatomical structures between animal models and humans, the presence of additional bacterial virulence and different persistence mechanisms. These mechanisms include intracellular survival within osteoblasts and fibroblasts, colonization of the osteocytic canalicular network, small-colony variant formation, enzymatic

degradation of host tissues and toxin production (46-48). Surgical debridement and mechanical removal of the biofilm are nonetheless considered essential for curing PJI with implant retention. Alternative biofilm removal or disruption methods such as thermal techniques, antimicrobial peptides, and electromagnetic approaches are currently under investigation, but these lie outside the scope of this thesis. If debridement is performed suboptimal (i.e., biofilm and persister cells remain present on the implant), the risk of relapse upon antibiotic cessation is high, even when 'biofilm-active' drugs are used. Within this conceptual framework, rifampicin's effectiveness likely stems from its potent bactericidal and intracellular activity against staphylococci rather than anti-biofilm properties.

If indeed monotherapy with drugs not considered 'biofilm-active' demonstrates similar effectiveness in PJI treated with DAIR, a paradigm shift in the concept of 'anti-biofilm antibiotics' is needed. This fits within the increasing body of evidence in which rifampicin was not superior to other antibiotics in the treatment of other staphylococcal (implant associated) infections, like prosthetic valve endocarditis and complicated *Staphylococcus aureus* bacteremia (49, 50). Such a finding challenges also the recommendations of both the Infectious Diseases Society of America (IDSA) and the European Bone and Joint Infection Society (EBJIS) to use or consider indefinite antibiotic treatment for patients suffering an acute PJI managed with DAIR-approach who were not treated with a "biofilm-active" drug (22, 51). The RICOTTA trial results will help clinicians determine whether both rifampicin-based as non-rifampicin-based treatment regimens can be considered as equally effective treatment regimens. A further advantage of having more oral antimicrobial options is the ability to tailor treatment to individual patients' needs. This benefit should not be underestimated. It is particularly relevant in an elderly PJI population with chronic comorbidities and polypharmacy, the globally rising antimicrobial resistance, and an increasing frequency of antibiotic shortages.

Antimicrobial treatment is one of the many prognostic factors in PJI. Other factors such as chronicity of infection, timing and quality of surgical debridement, causative pathogen, patient comorbidities, and quality of the bone and soft tissue are probably more strongly associated with outcome than the use of "biofilm-active" drugs (52-54). Nonetheless, to further optimize rational antimicrobial policies for patients treated with DAIR, high-quality data on the efficacy of different oral antimicrobial regimens are necessary. Given the rarity of this infection large multicenter trials are needed, like the RICOTTA trial and the RandOmised, Arthroplasty infection worldwide Multidomain Adaptive Platform (ROADMAP) trial. The ROADMAP trial is a large international Bayesian adaptive platform trial led by Australian researchers that aims

to investigate multiple important questions on PJI treatment (ClinicalTrials.gov ID NCT06771050).

Part 3: Suppressive antimicrobial therapy for prosthetic joint infections

The third part of this thesis investigated the concept and clinical application of suppressive antimicrobial therapy (SAT), a widely used strategy in prosthetic joint infection (PJI) management that remains largely unsupported by scientific evidence.

To identify worldwide differences in the practice of SAT in PJI and determine future research objectives we performed a global survey among PJI experts, detailed in **chapter 5**. The answers from 330 respondents across 42 countries showcased a large variety for SAT indication, preferred antimicrobial regimen, optimal dosing schedule, treatment duration and outpatient follow-up both within and between Europe, North America and Oceania. Notably, North American respondents were more inclined to prescribe SAT across a variety of clinical scenarios, whereas European respondents were more conservative. The survey also revealed that some physicians use SAT for a fixed treatment duration with a goal to increase chance of cure instead of suppression. This finding raises conceptual questions about the term "suppressive therapy" and its clinical implications. To further elucidate these differences in SAT practice and establish uniform definitions, we performed a systematic literature review, presented in **chapter 6.** Consistent with survey findings, the review that included 42 studies confirmed clear geographic variation: studies performed in North America frequently describe any use of oral antibiotics after DAIR, even for finite durations with curative intent, as SAT. Conversely, European studies usually reserve the term SAT for indefinite antimicrobial therapy aimed at relapse prevention in patients deemed incurable (e.g., chronic PJI treated with DAIR or without any surgery) or with unacceptable relapse risks (e.g., elderly or frail patients). This conceptual and semantic heterogeneity has practical consequences. When the same term is used for both curative and non-curative intent, study outcomes become difficult to interpret, and clinical recommendations increase the risk of being misapplied. To address this, a clear terminology is needed to differentiate between these two strategies. Based on expert consensus using a modified Delphi approach, two new definitions were proposed *to* improve clinical communication, future research comparability, and data interpretation.

Outcomes and Patient Risk Stratification

The overall pooled SAT success rate of 74% (95% CI 70%-79%) (n = 2467 patients), as reported in **chapter 6**, is surprisingly high given the complexity and refractory nature of many cases. We found no difference in outcome depending on the patient population that received SAT. On the other hand, in the cohort we analyzed in **chapter 7,**

we found that high-risk patients on SAT (i.e., late chronic PJI treated with DAIR or PJI treated without surgery) had a higher chance of relapse compared to patients with an acute PJI treated with DAIR in the presence of risk factors and patients in whom SAT was started because a relapse was deemed unacceptable. From a pathophysiological point of view: these patients likely differ in the presence of viable bacteria through several persistence mechanisms, as discussed above, such as biofilm-associated persisters and intracellular survival, from which latent infection may relapse. In all published observational studies, a subgroup of patients may have been cured already even before initiating SAT which has a positive effect on the reported outcome. This unknown proportion of patients already cured before the start of SAT probably differs between groups, complicating interpretation of SAT effectiveness. For that reason, we advocate that future studies stratify patients based on a prespecified risk of relapse if SAT would be withheld. To this end, we developed an expert-opinion–based risk classification, based on the findings of our systematic review, which stratifies patients into five risk groups.

Duration and Discontinuation of SAT

Despite the lack of supporting evidence, patients on SAT are frequently prescribed lower antibiotic doses than what is usually prescribed during the therapeutic treatment phase. Further, treatment discontinuation is also common, as described in **Chapters 5 and 6.** In **chapter 7,** these two treatment strategies were addressed by analyzing a cohort of 108 patients of high and medium risk patients with orthopedic implant infections—including PJI, fracture-related infections, and spinal implant infections—managed with SAT. We found an overall success rate of 69% and no difference between standardly dosed SAT and low dosed SAT. Furthermore, discontinuation of SAT after a median duration of two years in 25 patients with normalized inflammatory parameters and without symptoms appeared safe; only one patient (4%) who stopped therapy experienced relapse. This outcome did not change including only PJI and is in line with studies with comparable patient populations.

These findings are at odds with current dogmas that a PJI has to be suppressed as long as the biofilm (or the implant) is not removed and that antibiotics need to be dosed based on traditional PK/PD targets that take into account minimal inhibitory concentration (MIC) of planktonic micro-organisms. Moreover, it implies that biofilm and persister bacterial populations have a limited lifespan and can ultimately be cleared by host immunity after long-term antibiotic pressure.

Data on SAT discontinuation in patients with a higher risk of relapse remain sparse. Our findings support the possibility of safe SAT cessation even in high-risk patients

and are corroborated by a similar study by Pradier et al., which stopped SAT at two years in a comparable patient population (56). Other studies on optimal SAT duration after DAIR in diverse populations also reported that continuing antibiotics beyond one to two years does not further improve outcome (57-59).

Future research should therefore focus on identifying the conditions under which SAT can be safely discontinued, acknowledging that patients receiving SAT are highly heterogeneous with varying relapse risks. The key challenge is to determine which subgroups can safely stop therapy and which clinical, microbiological, and radiological parameters might guide this decision. Ideally, patients within predefined risk strata are randomized to either discontinue SAT after a fixed duration (e.g., two years) or continue indefinitely, to compare relapse rates and inform risk-based cessation strategies. In parallel, pharmacokinetic and pharmacodynamic studies should define new PK/PD targets to further optimize antimicrobial dosing in the context of suppression.

In conclusion, part 3 of this thesis underscores that, although SAT can be effective, treatment must be individualized. Uniform definitions of long-term antimicrobial therapy and careful patient stratification will be essential to reliably evaluate the effectiveness of different SAT strategies across diverse patient populations.

Pathophysiological concept of antimicrobial therapy for prosthetic joint infections

The findings in this thesis fit into, and further shaped, our understanding of the biofilm and persister cell dynamics during antimicrobial treatment of PJI. This theory is outlined in this final section of the discussion and summarized in Figure 1 (see also chapter 7), which depicts chronic PJI treated with DAIR and the interplay between antimicrobial therapy, biofilm and persister biology.

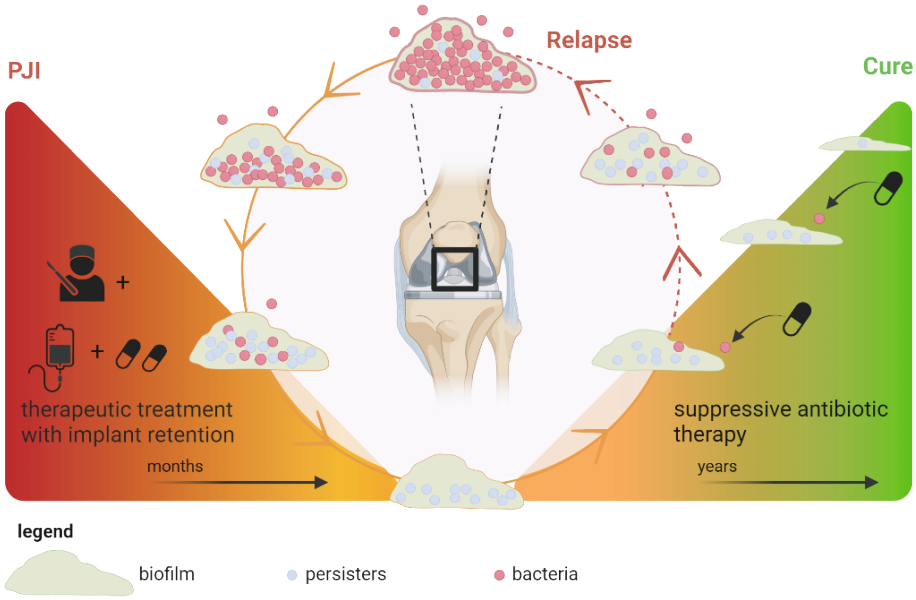

Figure 1. *Persister cell dynamics during suppressive antimicrobial therapy in chronic prosthetic joint infection managed with debridement, antibiotics and implant retention.*
Left triangle: Treatment of a chronic prosthetic joint infection with debridement and implant retention followed by therapeutic antimicrobial treatment. During this phase, all metabolically active bacteria in the (peri-)prosthetic tissue are killed but some persisters endure in the biofilm. Right triangle: Suppressive antimicrobial therapy (SAT) is only aimed at those bacteria that switch back from a persister state to a metabolically active state, thereby preventing spread into the periprosthetic tissue, which otherwise would lead to clinical relapse. For this specific goal, low-dose SAT could be sufficient. Under these conditions the biofilm slowly degrades and cure can be achieved. Reproduced from Chapter 7. Created with BioRender.com

We distinguish three (overlapping) phases of treatment of PJI. The initial phase takes place during the initial 6–12 weeks of antimicrobial therapy during which planktonic bacteria on the prosthesis surface and in adjacent bone and soft tissue are eradicated, essentially treating osteomyelitis. When persisters on the implant are thought

to remain, a second phase of treatment is warranted with long-term suppressive antimicrobial therapy because these persisters can revert to a planktonic state and reinvade peri-prosthetic tissue. SAT thus represents a period of sustained antimicrobial exposure in which all bacteria that revert to their metabolically active state are killed. This allows for the final phase: gradual reduction of the persister reservoir, presumably through natural decay—with a potential but uncertain role of host immunity.

To explain our finding that low-dose SAT regimens are effective, we assume that persisters occasionally switch back to a planktonic state in such small numbers that these can be eradicated with shorter cumulative time above the MIC (in case of β-lactams)—together with immune-mediated clearance—than is generally considered necessary for bone and joint infections.

The time required for complete clearance of persisters remains uncertain and likely depends on factors such as the infecting microorganism, initial bacterial load, soft-tissue conditions, and both systemic and local immune competence.

Concluding Remarks

Prosthetic joint infections are a complex and evolving challenge, requiring a careful balance of expertise of surgical and infectious diseases specialists. This thesis highlights that optimal management requires more than surgical skill or antibiotic selection—it demands multidisciplinary collaboration, integration of clinical, microbiological and pathophysiological knowledge, and patient-centered decision-making. In this thesis, clinical experience, critical appraisal of the literature, and observational data sets were integrated to advance our understanding of the antimicrobial management and treatment principles of prosthetic joint infections. Our findings challenge the widely assumed superiority of "biofilm-active" agents in patients treated with DAIR. In addition, it offers an explanation why suppressive antimicrobial therapy can be administered at a lower dose without losing effectiveness and safely discontinued after a certain time, even in high-risk patients. Nonetheless, uncertainties remain regarding optimal antimicrobial regimen, dosing, and treatment duration. In future research, clear stratification based on the probability of relapse of patients on SAT is needed to better answer these important clinical questions. Variability in international PJI practice and terminological inconsistencies further highlight the need for standardized definitions and global collaboration.

Looking forward, large multicenter randomized controlled trials, like the RICOTTA trial, will be essential to translate these insights into evidence-based guidelines aimed at reducing disease burden, decreasing antimicrobial consumption, facilitating patient-tailored therapy, and ultimately improving outcomes for patients affected by this devastating condition.

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Inleiding

Het vervangen van een versleten gewricht met een gewrichtsprothese is een zeer succesvolle en veelvoorkomende chirurgische behandeling. In Nederland leefden er in 2022 zo'n 800,000 mensen met een gewrichtsprothese. Helaas treedt bij 1-2% van de patiënten met een knie of heupprothese een geïnfecteerde gewrichtsprothese (prosthetic joint infection; PJI) op. Dit is een van de meest ingrijpende complicaties die kan ontstaan na het ontvangen van een nieuwe prothese. Deze infectie vormt een grote uitdaging voor zowel patiënten als zorgverleners en leidt altijd tot een langdurig en vaak complex behandeltraject. Deze bestaat uit een of meerdere operaties gecombineerd met langdurige antibioticatherapie en gaat vaak gepaard met meerdere ziekenhuisopnames. Voor de patiënt betekent dit een zware fysieke en mentale belasting, door onder andere pijn, onzekerheid en verlies van mobiliteit en zelfstandigheid. Naast de individuele impact op de patiënt brengt PJI ook aanzienlijke medische kosten met zich mee: in Europa ongeveer jaarlijks €350.000.000 en in de Verenigde Staten van Amerika wordt verwacht dat de kosten in 2030 oplopen tot het ongelooflijke bedrag van $1.850.000.000.

Bij een PJI veroorzaken metabool actieve bacteriën in het bot en de omringende weefsels een ontstekingsreactie, wat leidt tot de klinische symptomen. Een belangrijk pathofysiologisch kenmerk van PJI is de aanwezigheid van een zogeheten biofilm: een dun laagje bacteriën dat zich vasthecht aan het oppervlak van het kunstgewricht en zich omhult met een beschermende slijmlaag. Deze biofilm beschermt bacteriën deels tegen het immuunsysteem. Binnen deze biofilm kunnen de actieve bacteriën zich transformeren tot metabool nagenoeg inactieve bacteriën, zogenaamde persister cells. In deze toestand leiden ze niet tot een ontstekingsreactie en zijn ze niet gevoelig voor antibiotica. Hierdoor kunnen ze langdurig aanwezig blijven op de prothese. Daarnaast zijn ze in staat om na het stoppen van de antibioticabehandeling weer over te gaan in actieve bacteriën, wat vervolgens weer kan leiden tot opleving van de ontsteking en infectie. Dit is een belangrijk mechanisme dat bijdraagt aan het hardnekkige karakter van PJI.

Een PJI presenteert zich het vaakst acuut, meestal in de eerste weken na implantatie, met duidelijke tekenen van ontsteking zoals pijn, zwelling, roodheid en wondlekkage. In dit geval zijn er tijdens de operatie waarbij de prothese is geplaatst, helaas toch bacteriën in het operatiegebied gekomen. Een acute infectie kan ook later ontstaan en is dan het gevolg van een infectie waarbij er bacteriën in de bloedbaan zijn gekomen en vanuit daar secundair het gewricht infecteren.

Daarnaast kan een PJI ook chronisch verlopen, waarbij klachten zich langzaam ontwikkelen en pas maanden tot jaren na de operatie manifest worden, vaak met subtielere symptomen zoals aanhoudende pijn of functieverlies. In deze gevallen gaat het in de regel om minder agressieve bacteriën die langzaam groeien waardoor er een veel latere en mildere ontstekingsreactie op gang komt.

De behandeling van PJI is uitdagend, onder andere vanwege de bovengenoemde pathofysiologische kenmerken maar ook door andere ontwikkelingen. De patiëntenpopulatie met PJI wordt ouder en heeft daardoor vaker chronische aandoeningen waarvoor meerdere geneesmiddelen worden gebruikt. Tegelijkertijd is er een toename van antibioticaresistentie en komen antibioticatekorten steeds vaker voor. Een zorgvuldige afweging van de verschillende mogelijke behandelingen is dus essentieel en multidisciplinaire besluitvorming is daarbij een belangrijk instrument om de zorg voor patiënten met PJI te optimaliseren.

Een belangrijke behandelstrategie voor acute PJI is de zogenoemde DAIR, wat staat voor debridement, antibiotics and implant retention. Bij deze strategie wordt tijdens een operatie het geïnfecteerde weefsel verwijderd, de prothese grondig gereinigd maar niet verwijderd en nadien 6-12 weken antibiotica gegeven (eerst 1-2 weken via een infuus gevolgd door tabletten). Bij chronische PJI is voor genezing doorgaans vervanging van de prothese geïndiceerd. Wanneer dit niet haalbaar of niet wenselijk is, worden patiënten vaak langdurig (soms zelfs levenslang) behandeld met antibiotica om de infectie onder controle te houden. Deze behandelstrategie wordt aangeduid als suppressieve antimicrobiële therapie (SAT).

Dit proefschrift richt zich op deze vraagstukken rondom de antimicrobiële behandeling van PJI. In deze Nederlandse samenvatting worden achtereenvolgens onderzoeken naar multidisciplinaire zorg bij PJI, antimicrobiële behandelstrategieën bij DAIR en de toepassing van suppressieve antimicrobiële therapie besproken.

Deel I – Multidisciplinaire zorg bij bot- en gewrichtsinfecties

In 2015 werd in ons ziekenhuis een multidisciplinair overleg (MDO) opgericht om de zorg voor patiënten met PJI en andere bot- en gewrichtsinfecties te verbeteren. Tijdens dit wekelijkse MDO komt het multidisciplinaire team (MDT), bestaande uit orthopedisch en traumachirurgen, internist-infectiologen en medische microbiologen samen om patiënten te bespreken en samen tot behandeladviezen te komen. In **hoofdstuk 2** van dit proefschrift onderzochten wij hoe effectief dit MDT was. Dit hebben we gedaan door te analyseren in hoeverre de tijdens het MDO genomen beslissingen over de behandeling daadwerkelijk werden uitgevoerd door de behande-

lend arts. Deze zogeheten implementatiegraad van MDT-adviezen wordt beschouwd als een belangrijke maat voor effectieve multidisciplinaire besluitvorming, maar was tot nu toe niet onderzocht voor PJI. Over een periode van zeven jaar analyseerden wij 1321 behandelbeslissingen bij 509 patiënten, genomen tijdens 319 MDO's. De implementatiegraad bedroeg 92%, een percentage dat vergelijkbaar is met MDO's van andere medische specialismen. Dit bevestigt dat het MDT functioneert als een effectief instrument om tot breed gedragen behandelkeuzes te komen.

Wanneer werd afgeweken van een MDT besluit, betrof dit meestal behandeladviezen omtrent het type operatie (in tegenstelling tot adviezen voor antibiotica of diagnostiek). Het niet uitvoeren van dergelijke chirurgische adviezen bleek samen te hangen met slechtere klinische uitkomsten. In een deel van de gevallen speelde de voorkeur van de patiënt hierbij een rol. Sommige patiënten zagen af van een voorgestelde operatie om redenen die tijdens het MDO (nog) niet bekend waren. Dit onderstreept dat een behandelplan dat vanuit het perspectief van de artsen optimaal lijkt, niet altijd aansluit bij de wensen of overwegingen van de patiënt.

Hoewel afwijkingen van MDT besluiten slechts zelden voorkwamen, benadrukt dit het belang van het zorgvuldig afstemmen van behandelplannen op individuele patiëntvoorkeuren. Dit geldt met name bij ingrijpende chirurgische ingrepen en langdurige of belastende antibioticabehandelingen. Om patiëntvoorkeuren beter te integreren in MDO's kunnen verschillende benaderingen worden overwogen, zoals het betrekken van patiënten bij geselecteerde besprekingen of het inzetten van een gespecialiseerde verpleegkundige die patiëntwensen inventariseert en namens de patiënt inbrengt.

Een goed functionerend MDT kan bijdragen aan betere zorg voor patiënten door onder andere het vergroten van onderling begrip tussen specialismen, het verlagen van drempels voor overleg, het standaardiseren van behandelingen en follow-up en het gezamenlijk volgen van complexe patiënten. Daarnaast zijn er aanwijzingen dat multidisciplinaire zorg op de langere termijn kan bijdragen aan kostenreductie, bijvoorbeeld door kortere ziekenhuisopnames, het voorkomen van onnodige diagnostiek of chirurgie en een gerichter gebruik van antimicrobiële middelen.

MDO's kunnen daarom beschouwd worden als een belangrijk onderdeel van de behandeling van PJI en andere complexe bot- en gewrichtsinfecties. Hoewel de meest Nederlandse ziekenhuizen een MDO voor PJI hebben, is dit in andere landen lang niet altijd geval. In de VS gaat het om ongeveer 30% en in Europa breed 67%. Dit heeft onder andere te maken met het feit dat het opzetten en onderhouden van een

dergelijk team tijd, inzet en middelen kost. Het is daarom essentieel dat de meerwaarde van MDT's zo goed mogelijk wordt onderbouwd met data, om draagvlak te creëren bij zorgverleners en beleidsmakers. Dit zal moeten gebeuren door toekomstig onderzoek naar multidisciplinaire zorg dat verder kijkt dan alleen klinische uitkomsten. Aspecten zoals naleving van richtlijnen, aanwezigheid bij MDO's, kwaliteit van vastlegging van MDT besluiten, betrokkenheid van patiënten en kosteneffectiviteit verdienen eveneens aandacht. Door multidisciplinaire PJI zorg zo verder te ontwikkelen en te onderbouwen, kan de behandeling van patiënten verbeterd worden.

Deel II – Antimicrobiële behandelstrategieën bij PJI behandeld met DAIR
Het tweede deel van dit proefschrift richt zich op orale antibioticabehandeling bij patiënten met een PJI die worden behandeld met een DAIR-strategie. De keuze van de gerichte antibiotica in deze context is van groot klinisch belang, maar richtlijnen zijn momenteel nog gebaseerd op beperkt en tegenstrijdig wetenschappelijk bewijs.

Stafylokokken bacteriën zijn de meest voorkomende verwekkers van PJI. In nationale en internationale richtlijnen wordt bij stafylokokken-PJI die met DAIR worden behandeld al decennia een combinatiebehandeling met het antibioticum rifampicine aanbevolen, vaak in combinatie met een antibioticum uit de groep van de fluorchinolonen (bijvoorbeeld ciprofloxacine of levofloxacine). Deze aanbeveling is echter gebaseerd op een relatief smalle bewijsbasis.

De introductie van rifampicine als standaardbehandeling in de jaren negentig was voornamelijk gebaseerd op gunstige resultaten uit in-vitro-onderzoek, dierproeven en één kleine gerandomiseerde studie bij een zeer beperkt aantal patiënten met PJI (slechts 15). Meer recente klinische studies, waaronder een iets grote gerandomiseerde studie met 48 patiënten en een grote prospectieve observationele studie met 200 patiënten, hebben geen verschil in uitkomst laten zien tussen rifampicine-gebaseerde combinatietherapie en monotherapie. Deze studies waren echter ook underpowered en methodologisch beperkt, waardoor het trekken van definitieve conclusies niet mogelijk zijn.

Tegelijkertijd is behandeling met orale rifampicine-fluorchinolon combinatietherapie in de dagelijkse praktijk belastend voor veel patiënten. Tot 38% moet stoppen met de behandeling door bijwerkingen en/of geneesmiddelinteracties.

In **hoofdstuk 3** beschrijven wij het studieprotocol van de RICOTTA-studie, een multicenter gerandomiseerde klinische trial die momenteel in Nederland wordt uitgevoerd. In deze studie wordt onderzocht of gerichte orale monotherapie met clindamycine

niet inferieur is aan rifampicine-gebaseerde combinatietherapie tijdens de orale behandelfase van stafylokokken-PJI behandeld met DAIR. Naast het studieprotocol wordt in dit hoofdstuk uitgebreid stilgestaan bij methodologische en praktische aspecten van ons studieontwerp, met specifieke aandacht voor patiëntinclusie, een van de grootste uitdagingen bij onderzoek naar PJI.

Naast stafylokokken (die voornamelijk op de huid leven) kan PJI ook worden veroorzaakt door zogeheten Gram-negatieve bacteriën (die voornamelijk in de darmen leven). Bij deze infecties wordt bij DAIR aanbevolen om fluorchinolonen monotherapie als orale behandeling te gebruiken. Dit komt omdat deze antibiotica goed in bot en gewrichtsvloeistof komen en gunstige resultaten lieten zien in preklinische experimenten. Het bewijs voor deze aanbeveling is echter beperkt en tegenstrijdig. In **hoofdstuk 4** wordt de analyse gegeven van 74 patiënten met Gram-negatieve PJI uit een prospectief multicenter PJI-register van de regio Leiden. In deze observationele studie werd gekeken naar de effectiviteit van verschillende orale antibioticaregimes bij patiënten behandeld met DAIR. De resultaten suggereren dat er geen verschil is in uitkomst tussen patiënten die in de orale fase werden behandeld met fluorchinolonen en patiënten die werden behandeld met cotrimoxazol.

Cotrimoxazol vormt een praktisch alternatief voor fluorchinolonen vanwege vergelijkbare biologische beschikbaarheid, penetratie in bot en activiteit tegen veel Gram-negatieve bacteriën. Klinische gegevens over het gebruik van cotrimoxazol bij Gram-negatieve PJI zijn echter schaars en grotendeels beperkt tot kleine case series, waarin patiënten vaak ook tegelijkertijd andere antibiotica ontvingen. Zowel fluorchinolonen als cotrimoxazol kennen daarnaast relevante bijwerkingen, wat de noodzaak onderstreept van meerdere goed onderbouwde orale behandelopties.

Beperkingen van bestaand klinisch bewijs en het biofilmconcept

Veel observationele studies hebben geconcludeerd dat rifampicine bij stafylokokken-PJI en fluorchinolonen bij Gram-negatieve PJI geassocieerd zijn met betere uitkomsten. De vertaling van deze studies naar de klinische praktijk is echter lastig vanwege verschillende soorten van bias zoals confounding by indication, immortal time bias en selectiebias. Bovendien werden zelden goed afgebakende behandelstrategieën rechtstreeks met elkaar vergeleken. In plaats daarvan werd vaak één middel vergeleken met een heterogene restgroep, waardoor de effectiviteit van specifieke alternatieven mogelijk werd onderschat.

Een belangrijk thema in dit proefschrift is de discrepantie tussen veelbelovende preklinische resultaten en teleurstellende klinische uitkomsten van zogenoemde ‘bio-

film-actieve' antibiotica. Diermodellen laten zien dat rifampicine-bevattende combinatietherapie effectief kan zijn bij zeer jonge biofilms, maar dit effect verdwijnt wanneer biofilms ouder zijn. In de klinische praktijk zijn biofilms bij PJI meestal al één tot twee weken bestaand en vaak langer, waardoor volledige eradicatie door behandeling antibiotica alleen onwaarschijnlijk is. Daarnaast spelen bij patiënten andere mechanismen een rol die in diermodellen onvoldoende worden gerepresenteerd, zoals intracellulaire overleving van bacteriën, kolonisatie van het botkanaalnetwerk en variatie in bacteriële fenotypes. In dit licht is chirurgisch debridement en mechanische verwijdering van biofilm essentieel voor het succes van een DAIR-strategie. Wanneer dit onvoldoende gebeurt en persisterende bacteriën achterblijven, is het risico op recidief na het stoppen van antibiotica groot, ongeacht het gebruikte antibioticum. Binnen dit kader is het waarschijnlijk dat het klinische effect van rifampicine vooral berust op zijn sterke bactericide en intracellulaire activiteit tegen stafylokokken, en niet op unieke biofilm-eigenschappen. Als monotherapie met antibiotica die niet als 'biofilm-actief' worden beschouwd vergelijkbare uitkomsten laat zien, vraagt dit om een herziening van het concept van biofilm-actieve antibiotica in de behandeling van PJI.

Klinische implicaties

Dit deel van het proefschrift betoogt dat de huidige voorkeursbehandelingen bij DAIR niet onomstotelijk beter zijn dan alternatieve strategieën. Dit heeft belangrijke implicaties voor richtlijnen, waaronder aanbevelingen om langdurige of zelfs levenslang antimicrobiële behandeling te overwegen wanneer geen rifampicine of fluorchinolonen zijn gebruikt.

De resultaten van de RICOTTA-studie zullen bijdragen aan het bepalen of zowel rifampicine-gebaseerde als niet-rifampicine-gebaseerde orale behandelstrategieën als gelijkwaardig kunnen worden beschouwd. Het beschikbaar hebben van meerdere even effectieve orale behandelopties maakt het in ieder geval mogelijk om de therapie beter af te stemmen op individuele patiënten. Dit is bijzonder relevant bij de ouder wordende PJI-populatie met veel comorbiditeit en polyfarmacie, toenemende antimicrobiële resistentie en frequente tekorten aan antibiotica.

Om het antibioticabeleid bij DAIR verder te optimaliseren is hoogwaardig klinisch onderzoek noodzakelijk. Gezien de zeldzaamheid van PJI vraagt dit om internationale samenwerkingsverbanden en grootschalige multicenterstudies, zoals de RICOTTA-studies.

Deel III – Suppressieve antimicrobiële therapie
Het derde deel van dit proefschrift richt zich op suppressieve antimicrobiële therapie (SAT) voor PJI. Deze behandeling wordt doorgaans ingezet wanneer genezing van de infectie niet haalbaar wordt geacht na 6-12 weken antibiotica of wanneer het risico op een recidief na staken antibiotica als onacceptabel hoog wordt beschouwd. Deze behandelstrategie wordt veel toegepast er bestaan wereldwijd grote verschillen over de indicaties, behandelduur, optimale dosering en het beoogde doel van deze behandelstrategie.

Om inzicht te krijgen in de wereldwijde toepassing van SAT voor PJI en om lacunes voor toekomstig onderzoek te identificeren, voerden wij een internationale enquête uit onder orthopeden, infectiologen en medisch microbiologen die expert zijn op het gebied van de behandeling van PJI. In **hoofdstuk 5** worden de resultaten beschreven van deze enquête ingevuld door 330 respondenten uit 42 landen (voornamelijk Europa, Noord-Amerika en Oceanië). De uitkomsten laten een grote variatie zien in indicatiestelling, keuze van antimicrobiële middelen, doseringsschema's, behandelduur en poliklinische follow-up, zowel binnen als tussen Europa, Noord-Amerika en Oceanië. Noord-Amerikaanse respondenten waren over het algemeen vaker geneigd SAT voor te schrijven in diverse klinische situaties, terwijl Europese artsen deze strategie selectiever toepasten. Het meest uitgesproken verschil werd gezien bij patiënten met een acute PJI die met DAIR werden behandeld en geen duidelijke risicofactoren voor falen hadden: in Noord-Amerika werd in deze situatie relatief vaak nog SAT voorgeschreven, terwijl dit in Europa en Oceanië zelden gebeurde. Daarnaast liet de enquête zien dat een deel van de artsen SAT voorschrijft met een vooraf vastgestelde behandelduur en als doel de kans op genezing te vergroten, in plaats van de infectie te onderdrukken voor onbepaalde duur (soms levenslang). Deze bevinding roept fundamentele vragen op over de betekenis van het begrip "suppressieve therapie" en de klinische implicaties daarvan.

Om deze conceptuele verschillen verder te verduidelijken, voerden wij een literatuurstudie uit (systematic review) uit, beschreven in **hoofdstuk 6**. Deze review, waarin 42 studies over SAT bij PJI werden geïncludeerd, bevestigde de bevindingen uit de enquête en toonde opvallende geografische verschillen in het gebruik van SAT tussen de VS en Europa.

In Amerikaanse studies werd SAT vaak voorgeschreven bij patiënten waar niet duidelijk een reden voor SAT aanwezig was, behalve het feit dat de prothese nog in situ was gebleven (in tegenstelling tot het vervangen van de prothese). Ook werd elke vorm van orale therapie aangeduid met SAT, ook als er een intentie was om te genezen

en de behandelduur niet levenslang was maar 1 of 2 jaar. In de meeste Europese studies daarentegen werd SAT gebruikt voor langdurige of onbeperkte behandeling gericht op het voorkomen van recidief bij patiënten die als niet te genezen worden beschouwd, zoals bij chronische PJI behandeld met DAIR of zonder chirurgische interventie, of bij patiënten met een onacceptabel hoog recidiefrisico. De behandelduur voor deze patiënten was nagenoeg altijd dan ook levenslang. Deze conceptuele en semantische verschillen hebben belangrijke gevolgen. Wanneer dezelfde term ("SAT") wordt gebruikt voor zowel curatieve als niet-curatieve behandelstrategieën, wordt interpretatie van onderzoeksresultaten lastig en neemt het risico toe dat klinische aanbevelingen onjuist worden toegepast. Om dit probleem te adresseren, stelden wij op basis van expertconsensus, verkregen via een aangepaste Delphi-methode, twee duidelijke definities voor met als doel de klinische communicatie, de vergelijkbaarheid van toekomstig onderzoek en de interpretatie van uitkomsten te verbeteren:

1. Suppressieve antimicrobiële therapie = een niet-curatief antimicrobieel behandelregime dat wordt voortgezet langer dan de aanbevolen behandelduur volgens (inter)nationale richtlijnen, met als doel een latente infectie te onderdrukken (dat wil zeggen: het voorkomen van symptomen en de mogelijke gevolgen daarvan).

2. Verlengde antimicrobiële therapie= een antimicrobieel behandelregime met curatieve intentie dat gedurende een vaste periode langer wordt voortgezet dan de aanbevolen behandelduur volgens (inter)nationale richtlijnen, met als doel de kans op eradicatie van de infectie te vergroten zonder aanvullende chirurgie.

Om beter te kunnen bepalen voor welke patiënten SAT geschikt is, hebben wij daarnaast ook een risicostratificatie-model voorgesteld dat patiëntkenmerken, microbiologische factoren en chirurgische aspecten combineert om de kans op falen van de ingezette behandeling zonder suppressieve therapie in te schatten. Op basis hiervan kunnen patiënten worden ingedeeld in vijf risiconiveaus, wat een belangrijk raamwerk biedt voor toekomstig onderzoek en daarnaast kan helpen bij een meer onderbouwde keuze om wel of geen langdurige suppressieve therapie te starten in de klinische praktijk.

Ondanks het ontbreken van overtuigend bewijs worden patiënten die suppressieve antimicrobiële therapie (SAT) krijgen in de praktijk frequent behandeld met lagere doseringen dan tijdens de initiële therapeutische fase. Daarnaast blijkt uit onze enquête en literatuurstudie dat SAT ook regelmatig wordt gestaakt. In hoofdstuk 7 vergeleken wij lage dosering SAT met standaarddosering en onderzochten wij of SAT veilig kan worden gestopt in een cohort van 108 patiënten met PJI, fractuur-gerela-

teerde infecties en wervelkolom-implantaten infecties. Het overall succespercentage bedroeg 69%, zonder verschil tussen standaard- en lage dosering. Ook wanneer patiënten werden ingedeeld op basis van het risico op falen zonder SAT (waaronder een 'certain failure'- en 'high-risk'-categorie), werd binnen de 'certain failure'-groep geen verschil gevonden in falen tussen beide doseringsstrategieën, terwijl deze groep als geheel wel geassocieerd was met een hoger risico op falen. Daarnaast werd SAT bij 25 patiënten na een mediane behandelduur van twee jaar gestaakt, waarbij slechts één patiënt een recidief ontwikkelde. Deze bevinding bleef overeind in een analyse beperkt tot PJI en sluit aan bij andere studies met vergelijkbare patiëntpopulaties.

Deze resultaten staan haaks op het gangbare dogma dat een PJI onderdrukt moet worden zolang het implantaat aanwezig is, en dat antibiotica altijd volgens klassieke farmacokinetische en farmacodynamische principes moeten worden gedoseerd. De bevindingen suggereren dat biofilm- en persisterpopulaties mogelijk een beperkte levensduur hebben, maar het is op dit moment niet bekend welke mechanismen hieraan ten grondslag liggen en in hoeverre spontane afname van bacteriële vitaliteit hierin een rol speelt. Bovendien is onduidelijk in hoeverre deze bevindingen generaliseerbaar zijn naar andere kunstmateriaalinfecties, patiëntgroepen en micro-organismen.

Toekomstig onderzoek zou zich daarom moeten richten op het vaststellen van criteria voor veilig staken van SAT. Idealiter worden patiënten binnen vooraf gedefinieerde risicogroepen gerandomiseerd naar het staken of voortzetten van suppressieve therapie, om zo evidence-based strategieën te ontwikkelen.

Conclusies

PJI vormt een complexe en zich ontwikkelende uitdaging, waarbij een zorgvuldige balans nodig is tussen chirurgische en infectiologische expertise. Optimale behandeling vereist meer dan alleen chirurgie of antibioticakeuze en berust op multidisciplinaire samenwerking, integratie van klinische en microbiologische kennis en patiëntgerichte besluitvorming

In dit proefschrift zijn klinische ervaring, literatuur en observationele datasets gecombineerd om meer inzicht te krijgen in antimicrobiële behandelprincipes en de methodologie van antimicrobiële behandeling bij PJI. Onze bevindingen stellen de veronderstelde meerwaarde van 'biofilm-actieve' antibiotica bij patiënten behandeld met DAIR ter discussie. Daarnaast blijkt dat suppressieve antimicrobiële therapie vaak met lagere doseringen kan worden toegepast en in geselecteerde gevallen veilig kan worden gestaakt, ook bij patiënten met een verhoogd risico op falen

Tegelijkertijd blijven er onzekerheden bestaan over het optimale antimicrobiële regime, de dosering en de behandelduur. Toekomstig onderzoek vraagt om duidelijke risicostratificatie bij patiënten behandeld met SAT en om verdere standaardisatie van definities en methodologie. Grote, multicenter gerandomiseerde studies, zoals de RiCOTTA-studie, zijn essentieel om deze inzichten te vertalen naar evidence-based richtlijnen. Hiermee kan de ziektelast worden verminderd, het antimicrobieel gebruik worden beperkt, patiëntgerichte therapie worden gefaciliteerd en uiteindelijk de uitkomsten voor patiënten met deze ernstige aandoening worden verbeterd.

Portfolio

Description of academic development

I started my PhD journey in November 2022, while still working as a resident in internal medicine and infectious diseases. From the beginning, my research was closely connected to my clinical work: patients with prosthetic joint infections (PJI) pose serious challenges, and I wanted to contribute to improve the outcome of these patients. This combination of research and clinical care has shaped my PhD experience throughout.

My first study focused on the effectiveness of multidisciplinary care in orthopedic implant infections. I analyzed how effective our multidisciplinary meetings were and how they influenced patient management. This taught me how clinical practice could be systematically studied and improved. From there, my attention shifted to antimicrobial strategies. The most ambitious project was the RiCOTTA-trial, a large multicenter randomized controlled study. Coordinating this study, with 15 centers involved, meant writing protocols, securing ethical approvals, and building agreements across hospitals. It was my first experience with large-scale trial management: contracts, communication, and data integrity. Coordinating the RiCOTTA-trial strengthened my skills in leadership, logistics, and collaboration, and gave me insight into the organizational, ethical and legal complexity of clinical trials.

Alongside the trial, I worked on observational studies of antimicrobial regimens, and later expanded to international projects. A global survey among clinicians and a systematic review on suppressive antimicrobial therapy connected me to a worldwide network of colleagues. These studies underlined how differently prosthetic joint infections are managed across settings, and why open science practices such as preregistration matter. My PhD journey thus developed from a regional and national focus to international collaboration.

Throughout my PhD, I was actively involved in teaching and supervision. I supervised medical students during research projects (critical appraisal of topic), guided interns and residents, gave workgroup teaching sessions, and provided lectures for medical students and residents. Completing the University Teaching Qualification (BKO) formalized this work. Teaching deepened my own understanding, gave me of the joy of sharing knowledge and improved my ability to translate research questions into clinical practice and the other way around

My projects consistently relied on team science and close collaboration. Every study in this thesis was the result of a collaboration between orthopedic surgeons, clinical microbiologists, and infectious diseases specialists, often from different medical centers. The RiCOTTA trial in particular showed me what team science means in practice: aligning many partners, ensuring good data management, and keeping communication open. Later, I also became part of the editorial board of the Dutch Journal of Infectious Diseases (Tijdschrift voor Infectieziekten), which gave me a broader perspective on publication standards and peer review.

Disseminating research was another key part of my doctoral training. I presented findings at European Bone and Joint Infections Society annual meeting in Basel in 2023 and Barcelona in 2024 and at the European Congress of Clinical Microbiology and Infectious Disease in Barcelona in 2024. One of the highlights came in 2025 when I was invited by the president of the Musculoskeletal Infection Society of the United States to present my research at their annual scientific meeting in Newark, United States. That invitation, combined with collaborations on two international studies, showed me how research can open doors to new partnerships and exchange of ideas. These meetings not only increased visibility of our work but also sharpened my ability to present results to an expert (international) audience.

The practical side of research was equally instructive. Drafting trial protocols, preparing submissions to ethics committees, and managing contracts were demanding but an inevitable and vital part of science. These experiences taught me that research requires not only ideas and analysis but also persistence, organization, flexibility, teamwork and attention to detail. Managing a multicenter network also taught me that research is as much about organization and persistence as it is about people management.

Looking back, my PhD has been a period of growth on many levels. Scientifically, I developed from a curious resident into an independent researcher with experience in large multicenter randomized controlled trials, observational studies, global surveys, and systematic reviews. Professionally, I gained more confidence as a scientist, clinician, teacher, supervisor, and collaborator. Personally, I showed resilience and flexibility when necessary.

This PhD program will be an asset for my future as an infectious disease specialist.

All these skills I gained or improved—study design, multicenter coordination, critical appraisal, and multidisciplinary collaboration—will support my work in both clinical

practice and research. More importantly, it really showed me that research and patient care can go hand in hand. I will strive to improve outcomes for patients with complex infections, in both clinical care and research.

Dissemination table

Hanssen JLJ, Schakel GJ, Fontilus JM, Eeftinck Schattenkerk JK. Volwassenen met waterpokken in de tropen

Chapter in this thesis	Not in this thesis
Publication in peer reviewed journal	https://pubmed.ncbi.nlm.nih.gov/26934437/

Hanssen J, Berend K, Tai J, Vinke N. A haemodialysis patient with progressive leg pain

Chapter in this thesis	Not in this thesis
Publication in peer reviewed journal	https://njmonline.nl/article_ft.php?a= 1708&d=1135&i=194

Wijsman CA, Hanssen JLJ, Scheper H, Visser LG, van Lieshout L. A case of delayed diagnosis of East-African trypanosomiasis in a Dutch traveller

Chapter in this thesis	Not in this thesis
Publication in peer reviewed journal	https://doi.org/10.1093/jtm/tay024

Hanssen J, Toonen F. From dentist to internist

Chapter in this thesis	Not in this thesis
Publication in peer reviewed journal	https://www.njmonline.nl/article_ft.php?a=1941&d=1279&i=212

Hanssen JLJ, Delfos NM. A woman with skin rash and dyspnoea

Chapter in this thesis	Not in this thesis
Publication in peer reviewed journal	https://pubmed.ncbi.nlm.nih.gov/29192574/

Hanssen JLJ, Delfos NM, Hardi L. Uw diagnose? Hand-voet- en mondziekte

Chapter in this thesis	Not in this thesis
Publication in peer reviewed journal	https://www.tvionline.nl/journal-article/uw-diagnose-16/

Hanssen J, Planken E, Den Hartog W. Something is missing

Chapter in this thesis	Not in this thesis
Publication in peer reviewed journal	https://www.njmonline.nl/getpdf.php?id=2233

Hanssen JLJ, Anten S, Stollenwerck G, Kuijpers LM. Nontyphoidal Salmonella Osteomyelitis in an Immunocompetent Adult Without Preceding Symptoms

Chapter in this thesis	Not in this thesis
Publication in peer reviewed journal	*DOI:* 10.1097/IPC.0000000000000922

Hanssen JLJ, Stienstra J, Boers SA, Pothast CR, Zaaijer HL, Tjon JM, Heemskerk MHM, Feltkamp MCW, Arend SM. Convalescent Plasma in a Patient with Protracted COVID-19 and Secondary Hypogammaglobulinemia Due to Chronic Lymphocytic Leukemia: Buying Time to Develop Immunity?

Chapter in this thesis	Not in this thesis
Publication in peer reviewed journal	https://doi.org/10.3390/idr13040077

Hanssen JLJ, van der Wal RJP, van der Linden HMJ, van Prehn J, Scheper H, de Boer MGJ. Dosing and treatment duration of suppressive antimicrobial therapy in orthopedic implant infections: a cohort study

Chapter in this thesis	7
Conference contributions of the PhD candidate	Poster presentation at ECCMID 2024 Oral presentation at MSIS 2025
Publication in peer reviewed journal	https://doi.org/10.5194/jbji-9-149-2024

Hanssen JLJ, Gademan MGJ, Wouthuyzen-Bakker M, Davis JS, Dewar D, Manning L, Campbell D, van Prehn J, Miller AO, van der Wal RJP, van der Linden HMJ, Cortés-Penfield NW, Soriano A, de Boer MGJ, Scheper H. Global practice variation of suppressive antimicrobial treatment for prosthetic joint infections: A cross-sectional survey study

Chapter in this thesis	5
Conference contributions of the PhD candidate	Oral presentation at EBJIS 2023: https://boneandjoint.org.uk/Article/10.1302/1358-992X.2024.19.056 Oral presentation at MSIS 2025
Publication in peer reviewed journal	https://doi.org/10.1016/j.jinf.2024.106316

Hanssen JLJ, van der Wal RJP, Mahdad R, Keizer S, Delfos NM, van der Lugt JCT, Veldkamp KE, Nolte PA, Leendertse M, Gelinck LBS, Mollema FPN, Schippers EF, Wattel-Louis HG, Nelissen RGHH, Scheper H, de Boer MGJ. Targeted antimicrobial regimens for Gram-negative prosthetic joint infections: a prospective multicenter study

Chapter in this thesis	4
Publication in peer reviewed journal	https://doi.org/10.1128/aac.01232-24

Hanssen JLJ, van der Linden HMJ, van der Beek MT, van der Wal RJP, Termaat MF, de Boer MGJ, Scheper H. Implementation of multidisciplinary team decisions on the management of complex bone and joint infections: an observational study

Chapter in this thesis	2
Conference contributions of the PhD candidate	Oral presentation at EBJIS 2023, https://doi.org/10.1302/1358-992X.2023.17.053
Publication in peer reviewed journal	https://doi.org/10.1186/s12891-025-08329-0

Westgeest AC, Hanssen JLJ, de Boer MGJ, Schippers EF, Lambregts MMC. Eradication of community-onset Methicillin-resistant Staphylococcus aureus carriage: a narrative review

Chapter in this thesis	Not in this thesis
Publication in peer reviewed journal	https://doi.org/10.1016/j.cmi.2024.01.003

Hanssen JLJ. Effect van versmallen van breedspectrum-β-lactamantibiotica bij sepsis op antimicrobiële resistentie

Chapter in this thesis	Not in this thesis
Publication in peer reviewed journal	https://www.tvionline.nl/journal-article/effect-van-versmallen-van-breedspectrum-%CE%B2-lactamantibiotica-bij-sepsis-op-antimicrobiele-resistentie/

Jordans CCE, Vliegenthart-Jongbloed K, Osbak KK, Hanssen JLJ, van Beek J, Vriesde M, van Holten N, Dorama W, van der Sluis D, de Steenwinkel J, van Kampen J, Verbon A, Roukens AHE, Rokx C. Implementing HIV teams sustainably improves HIV indicator condition testing rates in hospitals in the Netherlands: the #aware.hiv clinical trial

Chapter in this thesis	Not in this thesis
Publication in peer reviewed journal	DOI: 10.1097/QAD.0000000000000416

Hanssen JLJ, van Hulten EY, Bos PK, van der Jagt OP, Lammers AJJ, Mahdad R, Nolte PA, Peters EJG, Poolman RW, Visser J, Somford MP, Veerman K, Vehmeijer SBW, Vlasveld IN, Zijlstra W, van Geenen R, Geurts J, Röling M, Wouthuyzen-Bakker M, Scheper H, de Boer MGJ; RiCOTTA study group. Rifampicin combination therapy versus targeted antimicrobial monotherapy in the oral antimicrobial treatment phase of staphylococcal prosthetic joint infection (RiCOTTA-trial): protocol for a randomized, controlled, open-label, non-inferiority trial

Chapter in this thesis	3
Conference contributions of the PhD candidate	Oral presentation at EBJIS 2024, https://doi.org/10.1302/1358-992X.2024.19.019 Oral presentation at MSIS 2025
Publication in peer reviewed journal	https://doi.org/10.1016/j.cct.2025.107972

L.W.M. Coenen, F.H. Tilmans, F.B. Achterberg, L.M.F. Kuijpers, M.E. Tushuizen, K.C.M.J. Peeters, drs. J.L.J. Hanssen. Uw diagnose? Toxisch megacolon

Chapter in this thesis	Not in this thesis
Publication in peer reviewed journal	https://www.tvionline.nl/journal-article/uw-diagnose-83/

Hanssen JLJ, Pijls B, Wouthuyzen-Bakker M, Manning L, Campbell D, van Prehn J, Miller AO, van der Linden HMJ, Ahl M, Cortés-Penfield NW, Soriano A, Boer MGJ, Scheper H. Practice variation, outcomes and definitions of suppressive antimicrobial therapy for prosthetic joint infections: a systematic review and expert consensus statement

Chapter in this thesis	6
Pre-registration	https://www.crd.york.ac.uk/PROSPERO/view/CRD420251011557
Conference contributions of the PhD candidate	Oral presentation at MSIS 2025
Publication in peer reviewed journal	https://doi.org/10.1093/cid/ciag251

Completed courses and other training

Mandatory activities		
Month/year	**Title**	**EC/hours**
10/2022	Basic course on Regulations and Organization of Clinical Trials (BROK)	1.5/42
2/2023	Basic Methods and Reasoning in Biostatistics	1.5/42
6/2023	Workshop Scientific Conduct for PhDs	0.2/5
12/2023	Leiden University Onboarding Programme Inform & Connect	0.4/10
Scientific courses, workshops and other training activities		
10/2023	Conference: annual meeting of the EBJIS, Basel	0.7/20
4/2024	Conference: ECCMID 2024, Barcelona	1/28
9/2024	Conference: annual meeting of the EBJIS, Barcelona	0.8/22
8/2025	Conference: annual scientific meeting of MSIS, Newark	0.4/12
Transferable skills courses, workshops and other training activities		
2022-2024	Course: University Teaching Qualification Leiden (BKO)	1.4/40
10/2022	Lecture at IBD course for gastro-enterologists	0.4/10
6/2023	Teaching: Guidance of Bachelor students Critical Appraisal of a Topic project	1/28
3/2024	Course: Communication in science	1.3/35
3/2024	Course: meta-analysis	1/28
5/2024	Teaching: workgroup emergency care for bachelor students medicine	0.1/4
6/2025	Teaching: workgroup infectious diseases for bachelor students medicine	0.1/4

Other scientific activities related to this thesis

Month/year	**description**	**Linked to chapter(s)**
10/2023	Oral presentation at EBJIS 2023, Basel	2
3/2024	Poster presentation at ECCMID 2024, Barcelona	7
9/2024	Oral presentation of research findings during weekly meeting of LUCID	4,5,7
9/2024	Oral presentation at EBJIS 2024, Barcelona	3
9/2024	Oral presentation at EBJIS 2024, Barcelona	5
8/2025	Oral presentation AT MSIS 2025, Newark	4,5,6,7

CRediT statement for the Chapters in this thesis

CRediT table for the thesis of Jaap Leonardus Jacobus Hanssen

Ch.	Type*	Short Title	Conceptualization	Data Curation	Formal Analysis	Funding Acquisition	Investigation	Methodology	Project Administration	Resources	Software	Supervision	Validation	Visualization	Writing – Original Draft	Writing – Review & Editing	Preregistered	Preprinted	Published with Peer Review
1	Introduction	introduction	■						■						■	■	☐	☐	☐
2	PhD project chapter	Multidisciplinary team for PJI	■	■	■		■	■	■				■		■	■	☐	☐	☑
3	PhD project chapter	RiCOTTA trial protocol	■	■					■						■	■	☐	☐	☑
4	PhD project chapter	Gram-negative PJI	■	■	■		■	■	■				■		■	■	☐	☐	☑
5	PhD project chapter	Survey on suppression for PJI	■	■	■		■	■	■		■		■		■	■	☐	☐	☑
6	PhD project chapter	review on suppression for PJI	■	■	■		■	■	■				■		■	■	☑	☐	☑
7	PhD project chapter	dosing of SAT for PJI	■	■	■		■	■	■				■		■	■	☐	☐	☑
8	Discussion	summary and general discussion	■						■						■	■	☐	☐	☐

**PhD project chapters are the direct result of the PhD project of the PhD candidate.*
Some theses also include Collaboration Chapters, to which the PhD candidate has contributed but fall outside the PhD project.

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Curriculum Vitae

Jaap werd op 3 maart 1986 geboren in Emmen. Hij groeide op in Broekland (Overijssel) met zijn ouders, Paul en Linda, twee broers, Joris en Bart en zijn zus Eljen. In 2004 deed hij eindexamen aan het Gymnasium van het Carmel College Salland en ging hij studeren in Groningen. Na het behalen van zijn propedeuse bewegingswetenschappen, startte hij in 2006 met de studie geneeskunde. Zijn coschappen liep hij in Groningen, Stadskanaal, Zwolle, Meppel en Oeganda en zijn semi-arts en wetenschapsstage bij de afdeling orthopedie van de Isala klinieken. Na het behalen van de master geneeskunde in 2013 deed hij een jaar klinische ervaring op als ANIOS Spoedeisende Hulp in de Isala Klinieken in Zwolle. Vervolgens werkte hij 15 maanden bij de afdeling interne geneeskunde in het St. Elisabeth hospitaal op Curaçao waar zijn enthousiasme voor de interne geneeskunde werd aangewakkerd. Bij terugkomst in Nederland ging hij als ANIOS interne geneeskunde in het Alrijne ziekenhuis in Leiderdorp aan de slag. In 2017 startte hij met de opleiding tot internist in het LUMC (opleiders prof. dr. H. de Fijter, prof. dr. N. Appelman). Hij deed zijn vooropleiding in het Alrijne ziekenhuis (opleider drs. S. Anten) en St. Elisabeth hospitaal, Curacao (opleider dr. K. Berend) waar zijn passie voor de infectiologie steeds meer toenam. Hij vervolgde daarom in 2021 de opleiding met het aandachtsgebied infectieziekten in Leiden en Den Haag (opleider dr. S. Arend) waar zijn interesse voor zowel het bewegingsapparaat als infecties samenkwamen in de behandeling van patiënten met orthopedische kunstmateriaal infecties. In november 2022 begon hij aan zijn promotietraject onder leiding van prof. dr. M.G.J. de Boer en dr. H. Scheper, internist-infectiologen. Omdat hij ook een bijzondere interesse heeft in onderwijs en opleiden, haalde tijdens de periode 2022-2024 de basiskwalificatie onderwijs (BKO).

Na het afronden van zijn opleiding in 2025 begon hij als internist-infectioloog in het LUMC en sinds 1 oktober 2026 is hij werkzaam als internist-infectioloog in Gelre ziekenhuizen. Daarnaast is hij hoofdredactielid van het Tijdschrift voor Infectieziekten. Hij woont in Naarden samen met zijn vrouw Nikki Vinke en hun twee kinderen, Isa en Mats.