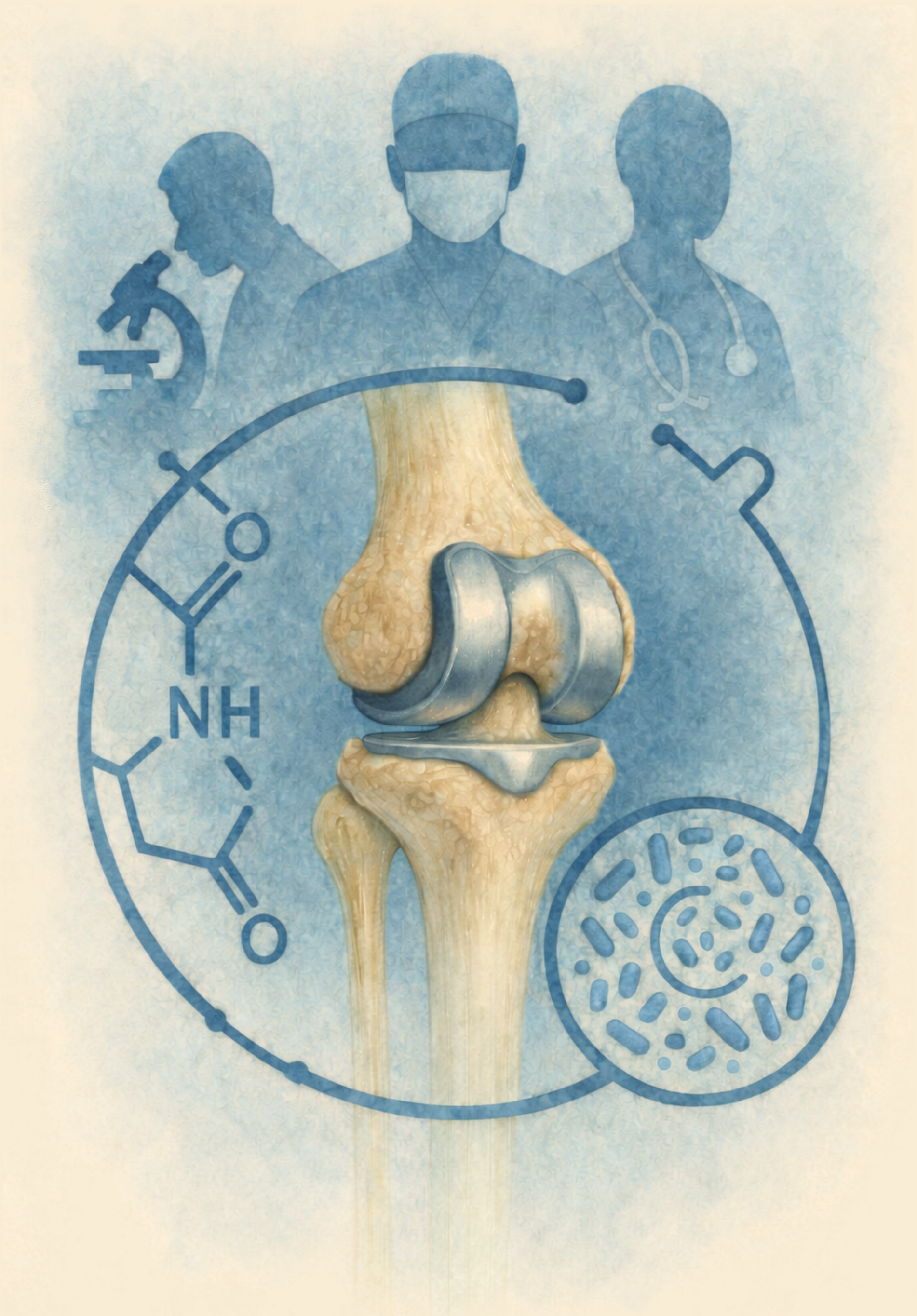
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Chapter 8

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.

8

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.

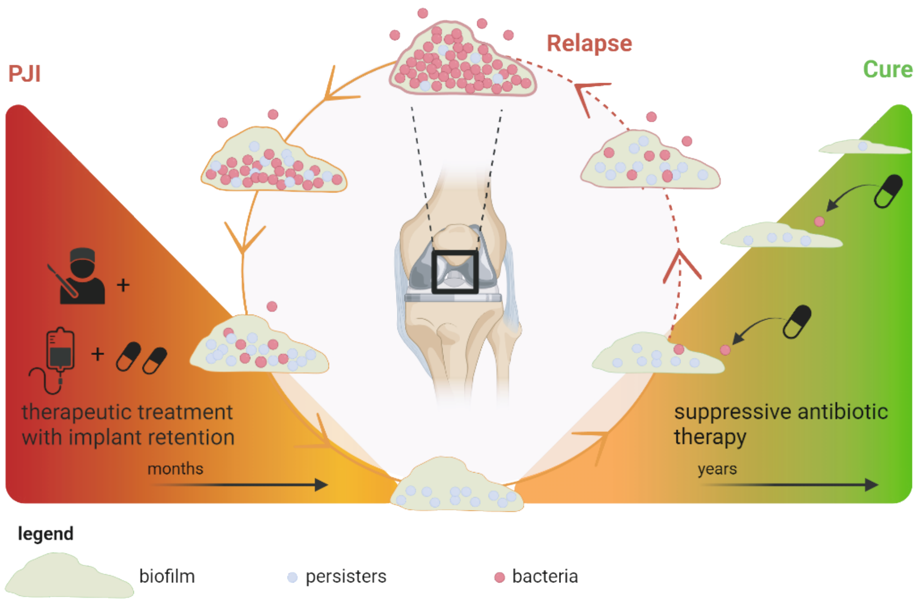

Figure 1. *Persister cell dynamics during suppressive antimicrobial therapy in chronic prosthetic joint infection managed with debridement, antibiotics and implant retention.*
Left triangle: Treatment of a chronic prosthetic joint infection with debridement and implant retention followed by therapeutic 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.

References

1. *Raine R, Wallace I, Nic a' Bháird C, Xanthopoulou P, Lanceley A, Clarke A, et al. Improving the effectiveness of multidisciplinary team meetings for patients with chronic diseases: a prospective observational study. Health Services and Delivery Research. 2014;2(37):1–172.*
2. *Awad F, Searle D, Walmsley K, Dyar N, Auckland C, Bethune R, et al. The Exeter Knee Infection Multi Disciplinary Team approach to managing prosthetic knee infections: A qualitative analysis. J Orthop. 2020;18:86–90.*
3. *Broom J, Broom A, Kenny K, Konecny P, J JP. Multidisciplinary team meetings in prosthetic joint infection management: A qualitative study. Infect Dis Health. 2023;28(3):145–50.*
4. *Soukup T, Lamb BW, Arora S, Darzi A, Sevdalis N, Green JS. Successful strategies in implementing a multidisciplinary team working in the care of patients with cancer: an overview and synthesis of the available literature. J Multidiscip Healthc. 2018;11:49–61.*
5. *Carlson VR, Dekeyser GJ, Certain L, Pupaibool J, Gililland JM, Anderson LA. Clinical Experience With a Coordinated Multidisciplinary Approach to Treating Prosthetic Joint Infection. Arthroplast Today. 2020;6(3):360–2.*
6. *Bauer S, Bouldouyre MA, Oufella A, Palmari P, Bakir R, Fabreguettes A, et al. Impact of a multidisciplinary staff meeting on the quality of antibiotherapy prescription for bone and joint infections in orthopedic surgery. Médecine et Maladies Infectieuses. 2012;42(12):603–7.*
7. *Walter N, Rupp M, Baertl S, Alt V. The role of multidisciplinary teams in musculoskeletal infection. Bone Joint Res. 2022;11(1):6–7.*
8. *Govaert GAM, Termaat MF, Glaudemans A, Geurts JAP, de Jong T, de Jong VM, et al. [Diagnosis and treatment of fracture-related infections]. Ned Tijdschr Geneeskd. 2019;163.*
9. *Kalson NS, Mathews JA, Alvand A, Morgan-Jones R, Jenkins N, Phillips JRA, et al. Investigation and management of prosthetic joint infection in knee replacement: A BASK Surgical Practice Guideline. Knee. 2020;27(6):1857–65.*
10. *Vuorinen M, Makinen T, Rantasalo M, Huotari K. Effect of a multidisciplinary team on the treatment of hip and knee prosthetic joint infections: a single-centre study of 154 infections. Infect Dis (Lond). 2021;53(9):700–6.*
11. *Sires JD, Pham K, Wilson CJ. The Impact of a Dedicated Multidisciplinary Team Approach for Prosthetic Joint Infections of the Lower Limb. Indian J Orthop. 2023;57(5):696–702.*
12. *Biddle M, Kennedy IW, Wright PM, Ritchie ND, Meek RMD, Rooney BP. Improving outcomes in acute and chronic periprosthetic hip and knee joint infection with a multidisciplinary approach. Bone Jt Open. 2021;2(7):509–14.*
13. *Karczewski D, Winkler T, Renz N, Trampuz A, Lieb E, Perka C, et al. A standardized interdisciplinary algorithm for the treatment of prosthetic joint infections. Bone Joint J. 2019;101-B(2):132–9.*
14. *Ntalos D, Berger-Groch J, Rohde H, Grossterlinden LG, Both A, Luebke A, et al. Implementation of a multidisciplinary infections conference affects the treatment plan in prosthetic joint infections of the hip: a retrospective study. Archives of Orthopaedic and Trauma Surgery. 2018;139(4):467–73.*
15. *Galsgaard A, Doorschodt T, Holten AL, Muller FC, Ploug Boesen M, Maas M. Artificial intelligence and multidisciplinary team meetings; a communication challenge for radiologists' sense of agency and position as spider in a web? Eur J Radiol. 2022;155:110231.*
16. *Misir A, Yuce A. AI in Orthopedic Research: A Comprehensive Review. J Orthop Res. 2025;43(8):1508–27.*
17. *Murtada A, Kayali F, Jubouri M, Ghattas SNS, Rezk SSS, Mir FA, et al. Artificial intelligence in colorectal surgery multidisciplinary team approach-From innovation to application. Physiol Rep. 2025;13(8):e70319.*

18. *Odone A, Barbati C, Amadasi S, Schultz T, Resnik DB. Artificial intelligence and infectious diseases: an evidence-driven conceptual framework for research, public health, and clinical practice. Lancet Infect Dis. 2025.*
19. *Roche JJ, Seyedshahi F, Rakovic K, Thu AW, Le Quesne J, Blyth KG. Current and future applications of artificial intelligence in lung cancer and mesothelioma. Thorax. 2025.*
20. *Li P, Wang Y, Zhao R, Hao L, Chai W, Jiying C, et al. The Application of artificial intelligence in periprosthetic joint infection. J Adv Res. 2025.*
21. *Manning L, Allen B, Davis JS. Design Characteristics and Recruitment Rates for Randomized Trials of Peri-Prosthetic Joint Infection Management: A Systematic Review. Antibiotics (Basel). 2023;12(10).*
22. *Osmon DR, Berbari EF, Berendt AR, Lew D, Zimmerli W, Steckelberg JM, et al. Diagnosis and management of prosthetic joint infection: clinical practice guidelines by the Infectious Diseases Society of America. Clin Infect Dis. 2013;56(1):e1–e25.*
23. *Zijlstra WP, Ploegmakers JJW, Kampinga GA, Toren-Wielema ML, Ettema HB, Knobben BAS, et al. A protocol for periprosthetic joint infections from the Northern Infection Network for Joint Arthroplasty (NINJA) in the Netherlands. Arthroplasty. 2022;4(1):19.*
24. *Zimmerli W, Widmer AF, Blatter M, Frei R, Ochsner PE. Role of rifampin for treatment of orthopedic implant-related staphylococcal infections: a randomized controlled trial. Foreign-Body Infection (FBI) Study Group. JAMA. 1998;279(19):1537–41.*
25. *Karlsen OE, Borgen P, Bragnes B, Figved W, Grogaard B, Rydinge J, et al. Rifampin combination therapy in staphylococcal prosthetic joint infections: a randomized controlled trial. J Orthop Surg Res. 2020;15(1):365.*
26. *Vollmer NJ, Rivera CG, Stevens RW, Oravec CP, Mara KC, Suh GA, et al. Safety and Tolerability of Fluoroquinolones in Patients with Staphylococcal Periprosthetic Joint Infections. Clinical Infectious Diseases. 2021;73(5):850–6.*
27. *Abdi-Ali A, Mohammadi-Mehr M, Agha Alaei Y. Bactericidal activity of various antibiotics against biofilm-producing Pseudomonas aeruginosa. Int J Antimicrob Agents. 2006;27(3):196–200.*
28. *Tanaka G, Shigeta M, Komatsuzawa H, Sugai M, Suginaka H, Usui T. Effect of the growth rate of Pseudomonas aeruginosa biofilms on the susceptibility to antimicrobial agents: beta-lactams and fluoroquinolones. Chemotherapy. 1999;45(1):28–36.*
29. *Thabit AK, Fatani DF, Bamakhrama MS, Barnawi OA, Basudan LO, Alhejaili SF. Antibiotic penetration into bone and joints: An updated review. International Journal of Infectious Diseases. 2019;81:128–36.*
30. *Widmer AF, Wiestner A, Frei R, Zimmerli W. Killing of nongrowing and adherent Escherichia coli determines drug efficacy in device-related infections. Antimicrob Agents Chemother. 1991;35(4):741–6.*
31. *Aboltins CA, Dowsey MM, Buising KL, Peel TN, Daffy JR, Choong PF, et al. Gram-negative prosthetic joint infection treated with debridement, prosthesis retention and antibiotic regimens including a fluoroquinolone. Clin Microbiol Infect. 2011;17(6):862–7.*
32. *Fantoni M, Borre S, Rostagno R, Riccio G, Carrega G, Giovannenze F, et al. Epidemiological and clinical features of prosthetic joint infections caused by gram-negative bacteria. Eur Rev Med Pharmacol Sci. 2019;23(2 Suppl):187–94.*
33. *Grossi O, Asseray N, Bourigault C, Corvec S, Valette M, Navas D, et al. Gram-negative prosthetic joint infections managed according to a multidisciplinary standardized approach: risk factors for failure and outcome with and without fluoroquinolones. J Antimicrob Chemother. 2016;71(9):2593–7.*
34. *Jaen N, Martinez-Pastor JC, Munoz-Mahamud E, Garcia-Ramiro S, Bosch J, Mensa J, et al. Long-term outcome of acute prosthetic joint infections due to gram-negative bacilli treated with retention of prosthesis. Rev Esp Quimioter. 2012;25(3):194–8.*

35. *Martinez-Pastor JC, Munoz-Mahamud E, Vilchez F, Garcia-Ramiro S, Bori G, Sierra J, et al. Outcome of acute prosthetic joint infections due to gram-negative bacilli treated with open debridement and retention of the prosthesis. Antimicrob Agents Chemother. 2009;53(11):4772–7.*
36. *Papadopoulos A, Ribera A, Mavrogenis AF, Rodriguez-Pardo D, Bonnet E, Salles MJ, et al. Multidrug-resistant and extensively drug-resistant Gram-negative prosthetic joint infections: Role of surgery and impact of colistin administration. Int J Antimicrob Agents. 2019;53(3):294–301.*
37. *Rodriguez-Pardo D, Pigrau C, Lora-Tamayo J, Soriano A, del Toro MD, Cobo J, et al. Gram-negative prosthetic joint infection: outcome of a debridement, antibiotics and implant retention approach. A large multicentre study. Clin Microbiol Infect. 2014;20(11):O911–9.*
38. *Wouthuyzen-Bakker M, Sebillotte M, Lomas J, Taylor A, Palomares EB, Murillo O, et al. Clinical outcome and risk factors for failure in late acute prosthetic joint infections treated with debridement and implant retention. J Infect. 2019;78(1):40–7.*
39. *Di Bonaventura G, Spedicato I, D'Antonio D, Robuffo I, Piccolomini R. Biofilm formation by Stenotrophomonas maltophilia: modulation by quinolones, trimethoprim-sulfamethoxazole, and ceftazidime. Antimicrob Agents Chemother. 2004;48(1):151–60.*
40. *Tornero E, Martinez-Pastor JC, Bori G, Garcia-Ramiro S, Morata L, Bosch J, et al. Risk factors for failure in early prosthetic joint infection treated with debridement. Influence of etiology and antibiotic treatment. J Appl Biomater Funct Mater. 2014;12(3):129–34.*
41. *Scheper H, de Boer MGJ. Comment on "Duration of rifampin therapy is a key determinant of improved outcomes in early-onset acute prosthetic joint infection due to Staphylococcus treated with a debridement, antibiotics and implant retention (DAIR): a retrospective multicenter study in France" by Becker et al. (2020). J Bone Jt Infect. 2020;6(1):17–8.*
42. *Scheper H, De Boer MGJ. Rifampin for Staphylococcal Prosthetic Joint Infection: Do We Still Need a Randomized Controlled Trial? Clin Infect Dis. 2022;74(7):1316–8.*
43. *Scheper H, van der Wal RJP, Mahdad R, Keizer S, Delfos NM, van der Lugt JCT, et al. Effectiveness of Different Antimicrobial Strategies for Staphylococcal Prosthetic Joint Infection: Results From a Large Prospective Registry-Based Cohort Study. Open Forum Infect Dis. 2022;9(10):ofac474.*
44. *Zimmerli W, Sendi P. Role of Rifampin against Staphylococcal Biofilm Infections In Vitro, in Animal Models, and in Orthopedic-Device-Related Infections. Antimicrob Agents Chemother. 2019;63(2).*
45. *Lucet JC, Herrmann M, Rohner P, Auckenthaler R, Waldvogel FA, Lew DP. Treatment of experimental foreign body infection caused by methicillin-resistant Staphylococcus aureus. Antimicrob Agents Chemother. 1990;34(12):2312–7.*
46. *Cai Y, Huang C, Chen X, Chen Y, Huang Z, Zhang C, et al. The role of Staphylococcus aureus small colony variants in intraosseous invasion and colonization in periprosthetic joint infection. Bone Joint Res. 2022;11(12):843–53.*
47. *Gunn NJ, Kidd SP, Solomon LB, Yang D, Roscioli E, Atkins GJ. Staphylococcus aureus persistence in osteocytes: weathering the storm of antibiotics and autophagy/xenophagy. Front Cell Infect Microbiol. 2024;14:1403289.*
48. *Rong Z, Chen X, Qin L, Wang X, Luo F, Zou Q, et al. Immune escape of Staphylococcus aureus mediated by osteocyte lacuna-canalicular network leads to persistent and uncured bone infection. Front Cell Infect Microbiol. 2025;15:1592086.*
49. *Ilges D, Shubeilat J, Nagarakanti SR. Should Rifampin Be Used to Treat Staphylococcal Prosthetic Valve Endocarditis? Mayo Clin Proc. 2024;99(7):1032–4.*
50. *Thwaites GE, Scarborough M, Szubert A, Nsutebu E, Tilley R, Greig J, et al. Adjunctive rifampicin for Staphylococcus aureus bacteraemia (ARREST): a multicentre, randomised, double-blind, placebo-controlled trial. Lancet. 2018;391(10121):668–78.*

51. *Sigmund IK, Ferry T, Sousa R, Soriano A, Metsemakers WJ, Clauss M, et al. Debridement, antimicrobial therapy, and implant retention (DAIR) as curative strategy for acute periprosthetic hip and knee infections: a position paper of the European Bone & Joint Infection Society (EBJIS). J Bone Jt Infect. 2025;10(2):101–38.*

52. *Hotchen AJ, Wismayer MG, Robertson-Waters E, McDonnell SM, Kendrick B, Taylor A, et al. The Joint-Specific BACH classification: A predictor of outcome in prosthetic joint infection. EClinicalMedicine. 2021;42:101192.*

53. *Cortes-Penfield N, Krsak M, Damioli L, Henry M, Seidelman J, Hewlett A, et al. How We Approach Suppressive Antibiotic Therapy Following Debridement, Antibiotics, and Implant Retention for Prosthetic Joint Infection. Clin Infect Dis. 2024;78(1):188–98.*

54. *Kristensen NK, Manning L, Lange J, Davis JS. External Validation of the Joint-Specific Bone Involvement, Antimicrobial Options, Coverage of the Soft Tissues, and Host Status (JS-BACH) Classification for Predicting Outcome in Periprosthetic Joint Infections: A Cohort of 653 Patients. J Arthroplasty. 2024;39(9):2352–6 e2.*

55. *Cortes-Penfield N, Beekmann SE, Polgreen PM, Ryan K, Marschall J, Sekar P. Variation in North American Infectious Disease Specialists' Practice Regarding Oral and Suppressive Antibiotics for Adult Osteoarticular Infections: Results of an Emerging Infections Network (EIN) Survey. Open Forum Infect Dis. 2024;11(6):ofae280.*

56. *Pradier M, Robineau O, Boucher A, Titecat M, Blondiaux N, Valette M, et al. Suppressive antibiotic therapy with oral tetracyclines for prosthetic joint infections: a retrospective study of 78 patients. Infection. 2018;46(1):39–47.*

57. *Escudero-Sanchez R, Senneville E, Digumber M, Soriano A, Del Toro MD, Bahamonde A, et al. Suppressive antibiotic therapy in prosthetic joint infections: a multicentre cohort study. Clin Microbiol Infect. 2020;26(4):499–505.*

58. *Nandi S, Doub JB, De Palma BJ, Potter GR, Stronach BM, Stambough JB, et al. Suppressive Antibiotic Therapy After Debridement, Antibiotics, and Implant Retention is Well-Tolerated Without Inducing Resistance: A Multicenter Study. J Arthroplasty. 2024;39(3):795–800.*

59. *Shah NB, Hersh BL, Kreger A, Sayeed A, Bullock AG, Rothenberger SD, et al. Benefits and Adverse Events Associated With Extended Antibiotic Use in Total Knee Arthroplasty Periprosthetic Joint Infection. Clin Infect Dis. 2020;70(4):559–65.*