Antimicrobial strategies and multidisciplinary care in prosthetic joint infections

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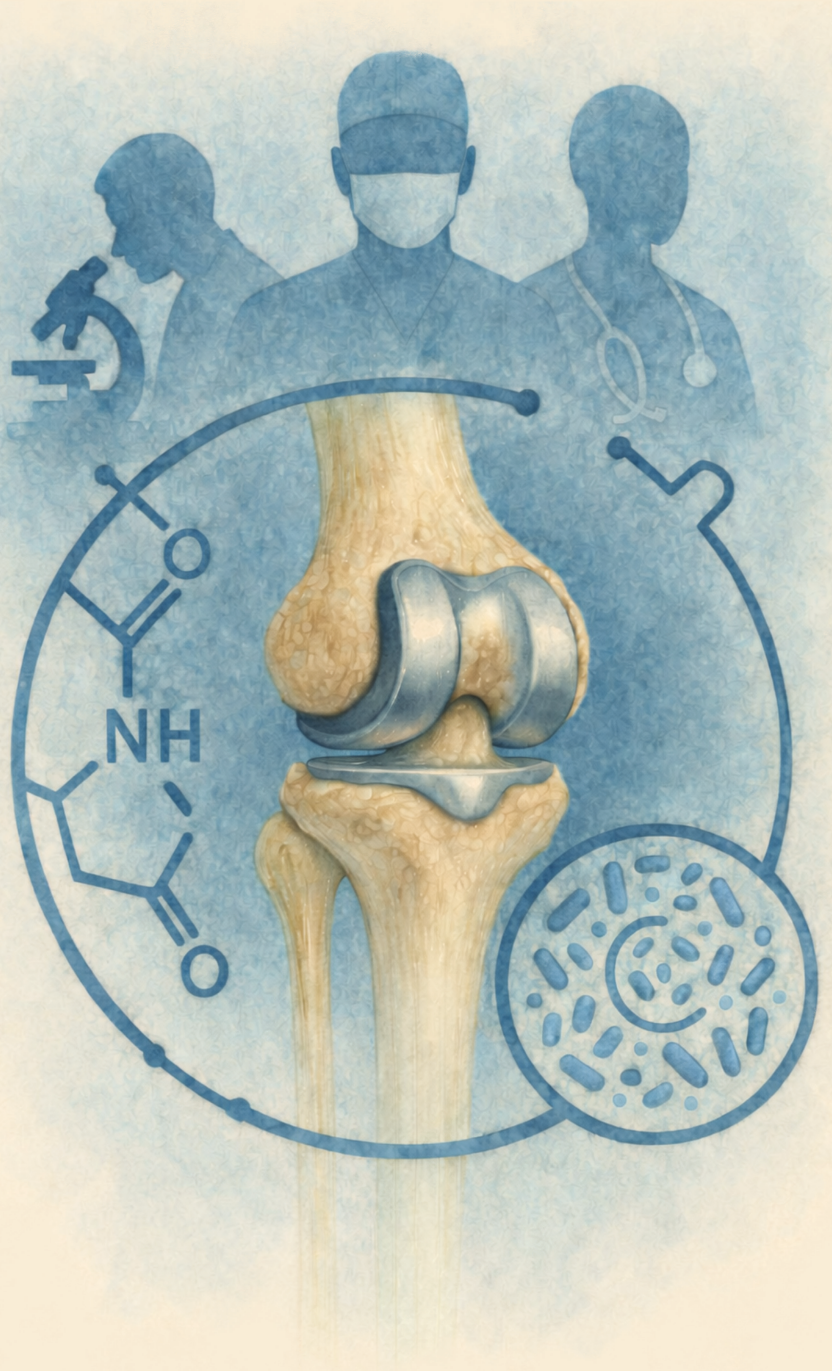
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Chapter 1

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.

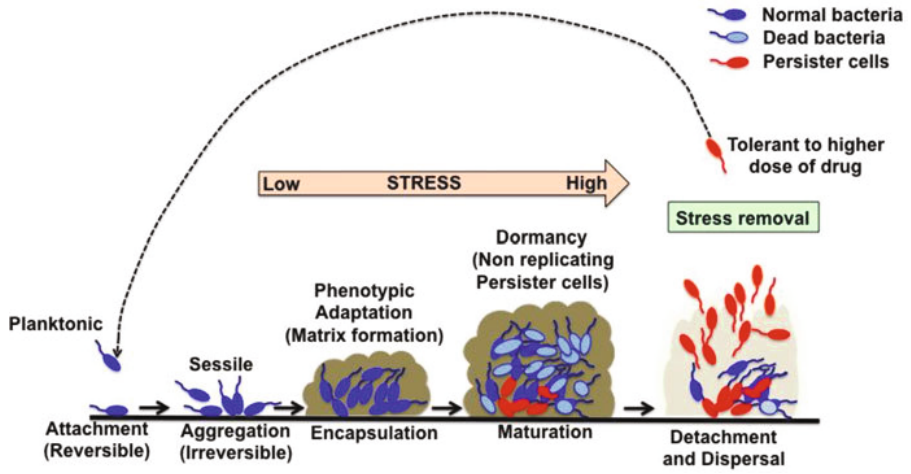

Fig 1. *Planktonic bacteria gradually form a biofilm and switch to persister cells under stress (e.g., antimicrobial therapy). When stress factors are withdrawn the persister cells switch back to active bacteria capable of causing infection. Figure from Alam, A., et al. (2019). Biofilms: A Phenotypic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