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Traitements antibiotiques oraux des infections de prothèses ostéoarticulaires à staphylocoque prises en charge par arthrotomie, synovectomie, lavage : revue systématique et méta-analyse en réseau

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ABRÉVIATIONS FRANCAISES

IPOA	Infection sur Prothèse Ostéoarticulaire ;
MAR	Méta-Analyse en Réseau
SOFCOT	Société Française de Chirurgie Orthopédique et Traumatologique
SPILF	Société de Pathologie Infectieuse de Langue Française
SARM	*Staphylococcus aureus* résistant à la méticilline

ABRÉVATIONS ANGLAISES

ASP	As Soon as results of the Preoperative Sample Culture were Available
BAS	Broad spectrum of B-lactam agent and agent active against methicillin-resistant *Staphylococus*
BWS	Broad spectrum without detail
CoNs	Coagulase Negative Staphylococcus
CRP	C-réactive protéine
DAIR	Debridement, Antibiotics and Implant Retention
GRADE	Grading of Recommendations Assessment, Development and Evaluation
IDSA	Infectious Diseases Society of America
JA	Joint Arthroplasty
ICM	International Consensus Meeting
NMA	Network Meta-analysis
NR	Not reported
NRCT	Non-Randomized Controlled Trial
NRS-R	Non-Randomized Studies – Retrospective
MCMC	Markov Chain Monte–Carlo
PJI	Prosthesis Joint Infection
PRISMA-P	Preferred Reporting Items for Systematic Reviews and Meta-analysis for Protocols
R_FQ	Rifampicin-Fluoroquinolone
R_CL	Rifampicin-Clindamycin
R_CO	Rifampicin-Cotrimoxazole
R_LI	Rifampicin-Linezolid
R_MI	Rifampicin-Minocycline
RCT	Randomized Controlled Trial
Rob2	Risk of Bias 2
ROBINS-I	Risk of Bias In Non-Randomized Studies - of Interventions
RR	Risk Ratio
SA	*Staphylococcus aureus*
SUCRA	Surface Under the Cumulative Ranking curve

INTRODUCTION

Epidémiologie et contexte

La prévention des infections est un enjeux clé dans la réduction des complications chirurgicales. Les sociétés de chirurgie et d'infectiologie se sont emparées de cette question depuis de nombreuses années et ont œuvré à la mise en place de stratégies visant à diminuer le risque d'infection du site opératoire. Néanmoins, malgré les efforts déployés et les progrès réalisés, 1 à 2 % des arthroplasties se compliquent d'infections [1, 2]. Bien que rare, l'infection sur prothèse ostéoarticulaire (IPOA) est une complication grave et est associée à une morbidité substantielle, à une augmentation des coûts médicaux et à une réduction de la qualité de vie des patients [3, 4]. Elle représente également un problème de santé publique croissant dans les pays développés en raison du nombre croissant d'arthroplasties [3].

Prise en charge des infections de prothèses ostéoarticulaires :

La prise en charge des infections de prothèses ostéoarticulaires nécessite une approche multidisciplinaire dans des centres spécialisés. Elle nécessite un diagnostic microbiologique fiable, une prise en charge chirurgicale adaptée ainsi qu'une antibiothérapie appropriée et prolongée.

Prise en charge chirurgicale :

Il existe plusieurs modalités de prise en charge chirurgicale :

1. Arthrotomie, synovectomie (« débridement »), lavage abondant (6 à 9L) et conservation de la prothèse. Cette prise en charge est recommandée dans le cadre d'une infection « aiguë », sans fistule et sans descellement. La synovectomie doit être réalisée par arthrotomie en reprenant la voie d'abord initiale. Pour effectuer une synovectomie complète, il est nécessaire de luxer la prothèse. Il est également recommandé de changer les pièces modulaires de la prothèse lorsque cela est possible. Le délai du caractère « aiguë » diffère en fonction des

recommandations. Ainsi, selon les recommandations de l'IDSA publiées en 2013, l'infection aiguë concerne les infections « aiguës post opératoire », qui surviennent dans un délai d'environ 30 jours après l'implantation de la prothèse, et les infections « aiguës tardives », correspondant à une infection hématogène et pour laquelle la prise en charge doit être inférieure à 3 semaines après l'apparition de symptômes infectieux [5]. Les recommandations de la société française de chirurgie orthopédique et traumatologie (SOFCOT) et de la société de pathologie infectieuse de langue française (SPILF) publiées en 2014 retiennent une durée inférieure à 15 jours entre la mise en place de la prothèse ou l'apparition des symptômes pour envisager une conservation de la prothèse [6]. Cependant, le délai du caractère « aiguë » a été remis en question depuis ces recommandations. Certains auteurs proposent de réaliser des arthrotomies, synovectomies, lavages jusqu'à 1 an après la mise en place de la prothèse articulaire [7].

2. Changement en un ou deux temps de la prothèse. Le changement doit être envisagé dans les situations considérées comme « aiguës », lorsqu'il existe une fistule, lorsque la prothèse apparait comme descellée ou si le nettoyage ne paraît pas macroscopiquement complet en per-opératoire. En dehors des infections « aiguës » un changement en un temps ou en deux temps avec mise en place d'un spacer est recommandé [5, 6]. Lorsque la prothèse est changée, un ciment imprégné d'antibiotiques est également recommandé. L'intérêt semble prophylactique en évitant une réinfection [8, 9] d'après les recommandations de la SPILF. Cependant, malgré l'absence d'essai clinique démontrant l'intérêt thérapeutique des ciments imprégnés d'antibiotiques, plusieurs propriétés *in vitro* et *in vivo* laissent présager d'une efficacité clinique. La combinaison de gentamicine et de vancomycine présente un intérêt microbiologique avec une activité synergique *in vitro* contre *Staphylococcus aureus* [10] et la combinaison de gentamicine et de clindamycine possède une activité anti-biofilm contre les bacilles gram négatifs [11].

Antibiothérapies recommandées :

Après la prise en charge chirurgicale, une antibiothérapie intraveineuse probabiliste large spectre, adaptée à l'épidémiologie locale et comprenant une béta lactamine et une molécule active contre les staphylocoques résistants à la méticilline est instaurée. Les recommandations de pratique clinique de la SPILF proposent plusieurs antibiothérapies probabilistes :

- Uréïdopénicilline/inhibiteur de bêta-lactamase et Vancomycine ; ou
- Céphalosporine de 3ème génération et Vancomycine ; ou
- Carbapénem (sauf ertapénem) et Vancomycine ; ou
- Céphalosporine de 3ème génération et Fosfomycine.

D'autres alternatives existent, notamment au centre de référence des infections ostéoarticulaires (CRIOAC) du CH de Tourcoing et du CHRU de Lille, où du Ceftobiprole ou une association de bêtalactamine à large spectre et de Daptomycine peuvent être proposés de manière probabiliste.

Cette antibiothérapie est ensuite adaptée aux résultats des prélèvements per-opératoires avec un relais par voie orale. Le délai de relais par voie orale tend à se réduire ces dernières années. L'IDSA recommandait, en 2013, un relais par voie orale après 2 à 6 semaines de traitement par voie intraveineuse [5] et la SPILF recommandait en 2014 un relais après 2 semaines [6]. Actuellement, de nombreuses équipes effectuent un relais dès l'identification bactérienne, soit environ 3 à 5 jours après la prise en charge au bloc opératoire [12].

Les *Staphylococcus aureus* et les staphylocoques à coagulase négative représentent respectivement 12 à 44 % et 30 à 47 % des microorganismes impliqués dans les infections sur prothèses ostéoarticulaires [13–15]. Les recommandations de l'IDSA privilégient l'utilisation d'un traitement antibiotique par voie orale comprenant la rifampicine et un autre agent avec une bonne diffusion osseuse. L'efficience du relais par voie orale a notamment été confirmée par

une étude publiée en 2019 [16]. Les compagnons à la rifampicine (900mg/24h ou 600mg/24h) recommandés par l'IDSA sont :

- En premier lieu : la ciprofloxacine (500mg/8h-750mg/12h) ou la lévofloxacine (750mg/24h).
- En second lieu, si les fluoroquinolones ne sont pas utilisables (absence de susceptibilité *in vitro*, allergies, intolérances) : la clindamycine (600mg/8h), la minocycline (100mg/12h) ou la doxycycline (100mg/12h), le linézolide (600mg/12h) ou le cotrimoxazole (160/800mg/8-12h) ou l'acide fusidique (500mg/8h) ou les céphalosporines orales de première génération (ex, céfalexine 100mg/kg en 3 prises).

Si la rifampicine ne peut pas être utilisée en raison d'une allergie, d'une toxicité ou d'une intolérance, le groupe d'experts de l'IDSA recommande 4 à 6 semaines d'une antibiothérapie intraveineuse. Les recommandations françaises publiées en 2014 proposent d'associer une fluoroquinolone avec de l'acide fusidique ou de réaliser une association clindamycine-acide fusidique.

La durée de l'antibiothérapie actuellement préconisée est de 3 mois, suite à la parution de l'étude de DATIPO en 2021 [17].

Problématique :

Les recommandations sur l'utilisation d'une association rifampicine-fluoroquinolone reposent principalement sur un essais clinique publié en 1998 par Zimmerli [18] qui comparait l'utilisation d'une bithérapie rifampicine-fluoroquinolone versus une monothérapie de fluoroquinolone. Cependant, alors que la rifampicine semblait être une pierre angulaire du traitement des IPOA depuis la parution des recommandations de l'IDSA en 2013, une remise en question de ce traitement a été faite en 2021 par un essais clinique randomisé comparant une bithérapie Rifampicine-Cloxacilline versus Cloxacilline en monothérapie [19]. De plus, lorsque les

fluoroquinolones ne peuvent être utilisées, il n'y a pas de consensus sur le compagnon de la rifampicine à utiliser, en dehors de l'importance d'utiliser une molécule à bonne diffusion osseuse. Enfin, lorsque la rifampicine ne peut être utilisée pour cause de résistance ou de contre-indication, aucune antibiothérapie par voie orale n'est recommandée par l'IDSA alors que la SPILF propose plusieurs associations.

Sur la base de ces constations, nous avons souhaité réaliser une revue systématique et une méta-analyse en réseau des traitements antibiotiques oraux des infections de prothèses ostéoarticulaires à staphylocoque traitées par arthrotomie, synovectomie, lavage et conservation de la prothèse afin d'établir une hiérarchisation des traitements.

Intérêt des méta-analyses en réseau :

Les méta-analyses en réseau (MAR) permettent de réaliser une analyse de la littérature en incluant tous les traitements évalués. Elles permettent de comparer des traitements qui n'ont pas été directement comparés lorsque les populations incluent dans les études sont comparables. Ainsi, si une étude compare le traitement A et le traitement B et qu'une autre étude compare le traitement B et le traitement C, nous pouvons comparer l'efficacité du traitement A et du traitement C (tout en prenant en compte que l'incertitude d'une comparaison indirecte est plus grande que celle d'une comparaison directe). Les MAR fournissent ainsi un aperçu de l'efficacité de tous les traitements disponibles évalués de manière similaire, sur des populations comparables, et permettent d'élaborer une hiérarchisation de ceux-ci [20].

Les méta-analyses en réseaux suivent une procédure d'analyse et d'écriture très formalisée par les recommandations de la Cochrane [21]. La question de recherche doit être déclarée à l'avance de leur réalisation sur le site PROSPERO. Ce travail tente de se rapprocher au plus près des méthodes modernes validées d'analyse de la littérature.

Objectif :

L’objectif de cette étude était de réaliser une MAR pour évaluer l’efficacité des traitements antibiotiques oraux disponibles pour le traitement des IPOA dues à des staphylocoques prises en charge par arthrotomie, synovectomie, lavage et conservation de l’implant ; et d’établir une hiérarchie de ces traitements.

ABSTRACT

Background

The management of prosthetic joint infection consists of a combination of surgery and antimicrobial therapy. The recommended oral antimicrobial regimen remains unclear, especially when rifampicin or fluoroquinolones cannot be used.

Methods

We performed a systematic review and network meta-analysis to obtain direct and indirect comparisons of trials. We searched MEDLINE, Embase, Web of Science, Cochrane Central Register of Controlled Trials, and ClinicalTrials.gov for published and unpublished trials from the creation of these databases until May 15, 2022. We included randomized controlled trials and non-randomized controlled trials of oral antimicrobial treatments for prosthetic joint infection due to *Staphylococcus* treated by debridement, antibiotics, and implant retention in adults (at least 18 years). We used the Cochrane Risk of Bias tool and Risk of Bias in Non-Randomized Studies – of Intervention to appraise trial methods. The primary outcome was remission, defined as the absence of local inflammatory symptoms, the absence of biological inflammatory syndrome, and the absence of relapse to the same bacteria.

Results

Of 2240 studies screened, 6 trials, 1 randomized controlled trial, and 5 non-randomized controlled trials which comprised 443 patients and 10 different treatments were included in the analysis. The overall quality of evidence was rated low. 6 regimens combined Rifampicin with another antibiotic: Fluoroquinolone, Clindamycin, Cotrimoxazole, Linezolid, Minocycline, Cloxacillin; 2 combined treatments without Rifampicin: Levofloxacin with Linezolid or Cotrimoxazole and 2 studies explored monotherapy: Linezolid or Cloxacillin. We were able to perform network meta-analysis in only 4 non-randomized controlled trials and on 5 different regimens because the number of patients included in other groups was too small. For remission

at 2 years, the combination Rifampicin-Fluoroquinolone was better than other combinations: Rifampicin-Clindamycin (risk ratio 1.08, 95% CI 0.76-1.90), Rifampicin-Mincocycline (risk ratio 1.13 CI, 95% 0.61-2.42), Rifampicin-Linezolid (risk ratio 1.10, CI 95% 0.69-1.94), Rifampicin-Cotrimoxazole (risk ratio 1.42, 95% CI 0.74-3.12), but did not reach significance. The remission rate was similar for the combination of Rifampicin-Clidamycin, Rifampicin-Mincocycline, and Rifampicin-Linezolid and was inferior to all other regimens for Rifampicin-Cotrimoxazole. Global heterogeneity of the entire network was low (p=0·81).

Conclusion

Among the oral antibiotic regimen for prosthetic joint infection due to *Staphylococcus* treated by debridement, antibiotics, and implant retention, a combination Rifampicin-Fluoroquinolone provides remission most frequently than other regimens but comparison did not reach significance. The quality of evidence is low and mostly based on non-randomized controlled trials. Alternative regimens with the best success rates were Rifampicin-Clindamycin, Rifampicin-Minocycline, and Rifampicin-Linezolid. Rifampicin-Cotrimoxazole should not be used unless there is no alternative. There is not enough data to evaluate a regimen without rifampicin. Efforts should be made to improve the level of evidence for combination treatment by evaluating the regimen through randomized controlled trials.

INTRODUCTION

Prosthetic Joint Infection(PJI) occurs in a minority of arthroplasties (1%–2%) [22] but represents a growing public health concern in developed countries as a result of the increasing number of operations for total joint arthroplasty [3]. Although rare, PJI is a serious complication, and such infection is associated with substantial morbidity, increased medical costs, and reduced quality of life [4, 23]. General principles of management of acute PJI include a multidisciplinary approach led by centers with expertise in this field. Reliable microbiological diagnosis, along with debridement implant retention, and prolonged appropriate oral antibiotic therapy, are key elements in the management of such infections [5, 16].

Most PJIs are caused by *Staphylococcus aureus* or Coagulase-negative staphylococci (CoNS) accounting for 12–44% and 30–47% respectively [13–15, 24, 25]. IDSA guidelines favor the use of an oral regimen including rifampicin and at least one other anti-staphylococcal agent [5]. Nevertheless, there is still a debate regarding the role of Rifampicin in staphylococcal PJIs and there is no consensus on its companion drug [19, 26]. All the more when Rifampicin can't be used due to resistance or contraindication, the hierarchies of another molecule according to their clinical effectiveness are still to be defined. Network meta-analysis (NMA) includes all treatment options within a single analysis and allows comparison of treatment that were not compared in head-to-head. It provides an overview of the efficacy of all treatments available and allows to hierarchize them.

The purpose of this study was to perform an NMA to assess the comparative efficacy of oral antimicrobial regimens available at present for the treatment of acute PJI due to Staphylococci and to obtain a treatment hierarchy.

METHODS

A protocol was prepared following the Cochrane Handbook [21] and the Preferred Reporting Items for Systematic Reviews and Meta-analysis for Protocols (PRISMA-P) [27].

Criteria for considering studies for this review

We defined study eligibility criteria using the PICOS (population, intervention, comparator, outcome, and study) design approach [28]:

Type of participants:

We included adults (aged 18 years or more) with evidence of PJI due to *S. aureus* or CoNS managed by debridement, antibiotics, and implant retention (DAIR). PJI due to *S. aureus* or CoNS was defined by one or more periprosthetic (intraoperative culture or preoperative synovial fluid aspiration culture) cultures positive to *S. aureus* or two or more periprosthetic cultures positive to CoNS. The patient had to be treated with a combination of antimicrobial agents administered intravenously during surgery and treatment modified subsequently according to the organism's antibiogram with oral antibiotic therapy. Studies with a lack of microbial documentation, studies including several types of infection and in which outcomes were not stratified by type of infection were excluded.

Type of intervention:

We aimed to compare oral antibiotic(s) regimens. We included studies comparing any of these treatments with each other or with a placebo. Studies using chronic suppressive antibiotics or investigating intravenous therapies alone or in combination with oral antibiotic regimens were excluded.

Outcome measure:

The main outcome was remission defined as the absence of local inflammatory symptoms, the absence of biological inflammatory syndrome, and the absence of relapse associated with the same bacteria. We anticipated that the duration of follow-up would be different between studies and therefore we included studies with one or two years of follow-up after the end of treatment.

Additional outcomes, evaluated 1 and 2 years after the end of the treatment, were death, the evaluation of the function of the joint with standard scales (like Oxford Hip and Knee Scores), and quality of life evaluated by a standard scale (like EuroQual-5D-3Lquestionnaire). Other additional outcomes, evaluated during the oral antimicrobial treatment, were adverse events, and adherence to antibiotic regimens.

Type of studies:

We included all experimental trials (randomized controlled, quasi-randomized controlled, nonrandomized controlled), quasi-experimental studies (interrupted time series, controlled before and after), and observational studies (cohort, case-control) focusing on any oral anti-microbial treatment of staphylococcal PJI managed by DAIR. We excluded study designs without a comparator group (e.g., case series) and expert opinion, reviews, and pooled analyses.

Information sources and literature search

We searched MEDLINE via Pubmed, EMBASE, and the Cochrane Central Register of Controlled Trials for randomized clinical trials published until May 15, 2022(Appendix 1: search strategy). BG also conducted a supplementary search of grey literature (ie, studies that are difficult to locate and unpublished studies) using the guide produced by the Canadian Agency for Drugs and Technologies in Health [29]. Grey literature sources that were searched included study registries (eg, the International Clinical Trials Registry Platform andClinicalTrials.gov), conference abstracts from the last 5 years, and tables of contents of the main journals that published on PJI in the last 10 years. The selected conferences included:

European Congress of Clinical Microbiology & Infectious Diseases, Idweek, European Bone and Joint Infection Society Annual Congress, and select journals included: Clinical Infectious Diseases, Clinical Microbiology and Infection, Journal of infectious Diseases, Clinical Orthopedics and related research, Journal of Bone and Joint Infection, Journal of Arthroplasty, Journal of Bone and Joint Surgery. References of the included studies will be also systematically searched for any additional relevant articles. We contacted experts in the field, including directors of the French Reference Centers for Complex Bone and Joint Infection (CRIOAC), to identify further reports of studies. No language restriction was applied and we included both published and unpublished studies.

Screening process

We downloaded abstracts retrieved into a reference management software, Zotero. Then, two authors (BG, OR) independently reviewed and assessed the eligibility of titles, and abstracts. We obtained the full text of Studies that were deemed relevant for review of their full texts and the two authors independently used the same inclusion criteria to determine eligibility. Any discrepancies were resolved through discussion with a third member of the review (ES). The process of study selection was documented in a PRISMA flow diagram.

Data analysis

Two authors (BG and OR) independently reviewed papers included in the final analyses and extracted relevant data directly from the paper, using a standardized data collection form (Appendix 2). Any discrepancies were resolved through discussion with another author (ES).

Risk of bias assessment

Results of the NMA were interpreted considering the risk of bias assessment of the included studies. Two investigators independently assessed the methodological quality/risk of bias of the studies that fulfill the eligibility criteria. Disagreements regarding quality items were discussed and resolved through consensus with a third investigator.

The Cochrane Risk of Bias 2 (Rob2) tool [30], for RCT, and The Risk Of Bias In Non-Randomized Studies – of Interventions (ROBINS-I tool), for NRCT, were used by the two authors (BG and OR) to assess the quality of studies.

Strategy for data synthesis

Given that considerable heterogeneity among treatment schemes was expected, with very few studies performing a direct pairwise comparison, we planned to explore the feasibility of pooling comparative data on the various antibiotic treatment schemes using Bayesian pairwise meta-analysis and NMA. All outcomes of interest were dichotomous data, therefore, we planned to calculate the pooled risk ratio (RR) with 95% confidence intervals (Cis) [31].

We conducted a Bayesian random-effects network meta-analysis (NMA) using Markov Chain Monte–Carlo (MCMC) Methods developed by Lu et Ades [32]. We limited the study to oral antimicrobial treatment with at least 3 patients following the same regimen. We represented graphically the network, with nodes representing the interventions, and edges, the available direct comparisons between interventions. Clinical and methodological heterogeneity was evaluated by checking the characteristics and design of the included studies. To assess consistency, we performed a node split analysis [33] and reported the estimates of Bayesian NMA as rank probabilities to identify the relative rankings of antimicrobial treatments based on the surface under the cumulative ranking curve (SUCRA) and its 95% credibility interval [34].

Surveys with at least a year of follow-up were included. Our main analysis concerned the outcome at 2 years. A first network analysis was performed on the whole data. Then, to leverage the impact of the study with a lower follow-up, we added 5% of relapse in the studies with a follow-up between 1 and 2 years. These relapses were added to each treatment group for a sensitivity analysis.

We did all analysis using R version 4.1.1 and the package gemtc.

Finally, we used the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system for rating the overall quality of evidence [35]. Grade has issued guidance on network meta-analysis [36].

The study protocol was registered a priori with PROSPERO (registration number CRD42022283265).

RESULTS

Results of the search

We identified 2240 references, of which 843 were duplicates (figure1). After reviewing the titles and abstracts of all available, references were excluded because it was animal studies, editorial letter, case report, literature review, or article was not related to the topic in terms of population, intervention or outcome. Only 102 full-texted articles were reviewed to evaluate their accordance with the inclusion criteria. Of the 102 full-text articles reviewed, 6 publications (1 RCTs and5 NRCTs) were deemed eligible after applying inclusion and exclusion criteria. The studies were mainly excluded because the study populations mixed infections on osteoarticular prostheses, on osteosynthesis material, and infections treated by DAIR or by prosthesis change without presenting the results for these subgroups. One additional unpublished RCT was retrieved from clinical trial. The protocol was published in October 2020, started on November 2021 and it's still recruiting with an estimated study completion date: June 2027 [37]. All trials were in English. The PRISMA flow chart shows the results of the screening and selection of studies (see Figure 1) [38].

Included studies

We included 6 studies in the systematic review, 1 RCT and 5 NRS. RCT published by Karlsen in 2020 was performed between 2006 and 2014 in 8 centers in Norway. The 5 NRS were published between 2006 and 2021. Most of the recruitment periods were between 2000 and 2010 and the most recent period was between 1997-2017. Evidence was based on Spanish, French, Portugal, USA, and Netherlands researches (3 of them were developed by Spanish [39–41] teams, 1 by a Netherland [42] team and 1 by a French [12] team). Four studies were conducted in a single hospital [12, 39–41]l, while only 1 study was multicentric with 8 centers [42]. All studies were retrospective observational studies. A half were case-control studies [12, 40, 41] with the primary objective of investigating risk factors associated with PJI treatment failure, other were retrospective cohort studies.

The full list of the studies included and a summary of the characteristics of these studies are displayed in table 1.

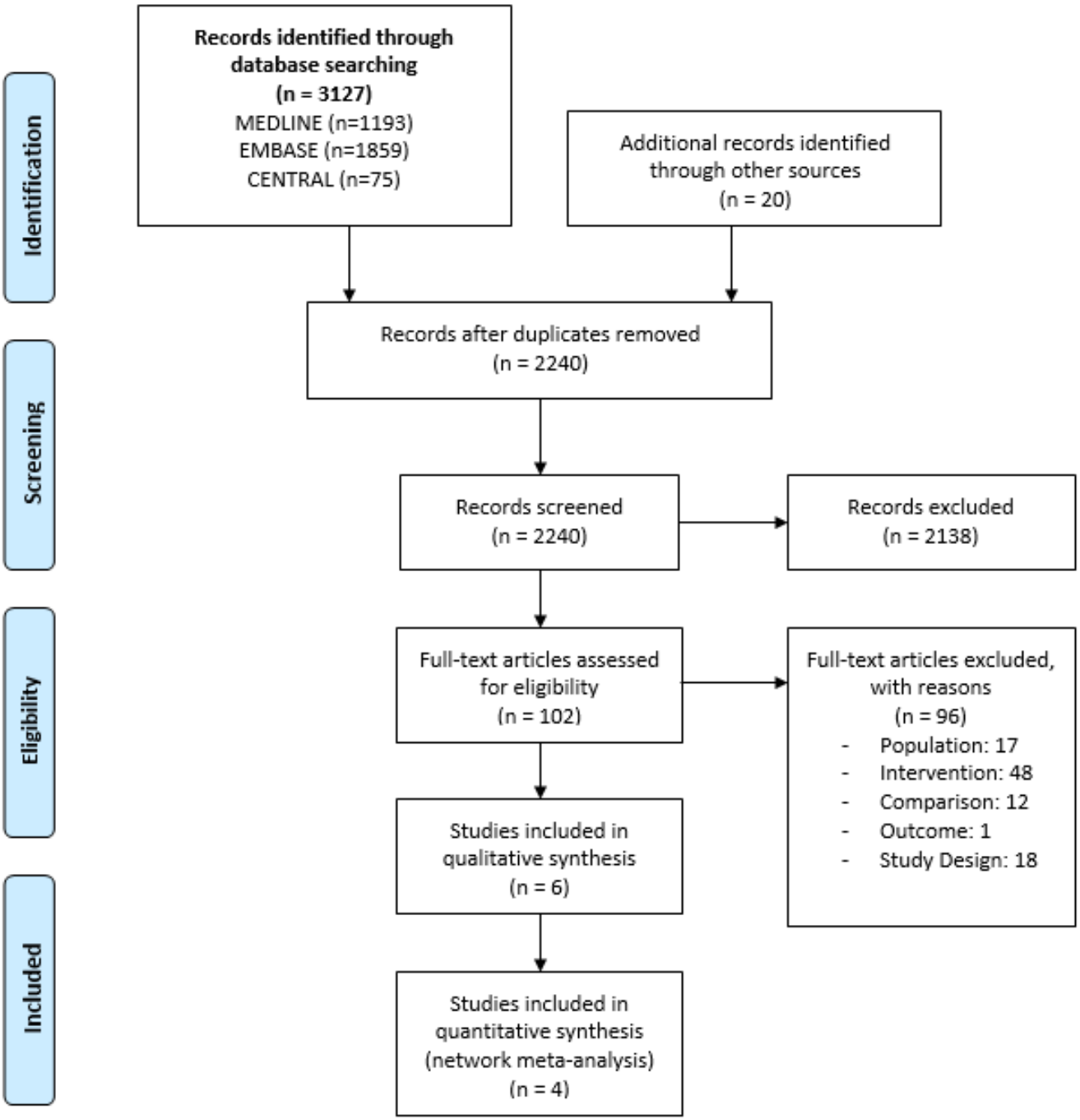


Figure 1. Study selection PRISMA 2009 Flow Diagram

Patients and infection characteristics

All studies focused on adults. A study published by Karlsen included *S. aureus* and CoNS with or without methicillin resistance. This study included 48 patients but only 38 patients were treated with oral antimicrobial treatment. Only staphylococcal species without methicillin resistance were treated with an oral microbial regimen, staphylococcal with methicillin resistance were treated with intravenous vancomycin. Hip or knee PJI was suspected when patients presented with pain, redness, or wound discharge within 30 days after prosthetic surgery (acute postoperative PJI) or with symptoms for less than 3 weeks (acute hematogenous PJI) and confirmed with at least two of the height specimens performed during surgery positive with the same microbe.

Concerning NRS, the total population was 405 patients with PJI due to staphylococcal treated by DAIR and oral antimicrobial therapy. The mean study size (number of patients included) was 81 but only one study included more than 60 patients [42]. All studies used at least the microbiological criteria described in the study selection method to define PJI. No study used the same diagnostic criteria and only the most recent study used international guidance criteria for the diagnostic of PJI [42](table1). All studies included Hip and knee prostheses infections, but none of the studies included shoulder prostheses infections. Three studies included only *S. aureus* infection [12, 40, 42], 2 studies included *S. aureus* and CoNS [39, 41]. Three studies included staphylococci with methicillin resistance [12, 40, 41] and the two others did not report this characteristic [39, 42].2 studies included only monomicrobial infection [39, 40] and the 3 others included monomicrobial and polymicrobial infections. For details, see table 1. All PJI included in the systematic review were managed with DAIR. As most of the recruitment periods were before the publication of IDSA guidelines (2013), the indication of DAIR was based on different definitions of acute prosthetic joint infection (table 1).

Concerning DAIR, only 3 studies reported that modular components were changed for all patients [19, 40, 41], 1 study that they were not changed for all patients [42] and the 2 other studies did not report its intervention. A combination of antimicrobial agents administered intravenously was begun after the DAIR procedure for all studies [39, 42]. 4 studies report that they used a broad-spectrum B-lactam agent and a second antimicrobial agent with activity against methicillin-resistant staphylococci [12, 39–41]. One study mentioned that they used a broad spectrum without details [39] and another mentioned that it was following local protocol [42]. The time to switch to definitive oral antibiotic therapy was not standardized for 1 study and was left to the judgment of the clinician [39]. For 1 team, the switch to oral therapy was performed as soon as results of the per operative sample culture were available [12], for 2 other studies, the switch was done after 10 days [40, 41], and for the most recent it was 14 days minimum after surgery [42]. The total duration of treatment was 2–3-months for Soriano et al[39], according to Zimmerli algorithm [18] (3 months for Hip and 6 months for Knee) for Senneville et al [12], and 3 to 6 months for Beldman et al [42]. For the two others duration of antibiotics was not standardized by an internal protocol and left to the discretion of the clinician. For details, see Table 2.

Table 1. Studies Characteristics & description of PJI included in studies (*CoNs: Coagulase Negative Staphylococcus; CRP: C-Reactive Protein; DAIR: Debridement, Antibiotics and Implant Retention; ICM: International Consensus Meeting*; *JA: Joint Arthroplasty*; NR: Not reported; *NRS-R: Non-Randomized Studies – Retrospective; PJI: Prosthesis Joint Infection; RCT: Randomized controlled study; SA: Staphylococcus aureus)*

Study	Study design	Number of centres	Countries	Period of recrutement	Definition of PJI	Localisation prosthesis	Timing	Bacteriology	Methicillin-resistant	Polymicrobial
Karlsen (2020)	RCT	8	Norway	2009-2012	Pain, redness, or wound discharge with at least two of the height specimens performed during surgery positive with the same microbe	Hip & Knee	1. Acute postoperative : 30 days after prosthetic surgery 2. Acute hematogenous : symptoms for less than 3 weeks	SA & CoNS	No	No
Soriano(2006)	NRS-R	1	Spain	NR	Inflammatory signs, Increased levels of C-reactiveprotein, and, Yielded pathogenic microorganisms from deep samples, and ⁄ or pus was present.	Hip & Knee	<30days after joint arthroplasty	SA & CoNS	Yes	No
Vilchez(2010)	NRS-R	1	Spain	2000-2007	Presence of local inflammation of acute onset, Macroscopic evidence of extension of the infection through the capsule during debridement and, Isolation of S. aureus in deep samples.	Hip & Knee	Symptoms <15 days of duration during the first 2 months after joint arthroplasty	SA	NR	No
Senneville(2011)	NRS-R	1	France	2000-2006	Isolation of ≥1 strain of S.aureus from a reliable sample taken from the prosthetic site	Hip & Knee	Symptoms < 4 weeks	SA	Yes	Yes
Tornero(2013)	NRS-R	1	Spain	1999-2009	Presence of local inflammation, Macroscopic evidence of extension of the infection through the capsule during open debridement and, Isolation of significant microorganisms from deep samples	Hip & Knee	<30days after joint arthroplasty	SA & CoNS	Yes	Yes
Beldman(2021)	NRS-R	8	Spain/Portugal/ USA/Netherlands	1999-2017	ICM 2018	Hip & Knee	1. Early acute (post-surgical): Symptoms < 90 days after joint arthroplasty. 2. Late acute: acute onset of symptoms occurring >90 days after joint arthroplasty in a prior asymptomatic joint.	SA	NR	Yes

Table 2. Management of PJI outside of oral antimicrobial treatment *(ASM: As Soon as results of the Microbial identification was available; BAS: Broad spectrum of B-lactam agent and agent active against SARM; BWS: Broad spectrum without Detail; NR: Not reported)*

Study	Exchange of mobile components	Empircal antimicrobial regimen	Detail	Time to switch to oral treatment	Total Duration of treatment
Karlsen (2020)	Yes	BAS	Cloxacillin (2 g/6h) and Vancomycin (1 g/12h)	2 weeks	6 weeks
Soriano (2006)	NR	BWD	No detail	Not reported	2–3 months - continued until resolution of clinical signs and normalisation of CRP levels (< 1 mg⁄ dL)
Vilchez (2010)	Yes	BAS	Ceftazidime (2 g/8 h) + Vancomycin (1 g/12 h)	10D	Not standardized
Senneville (2011)	NR	BAS	Cefotaxime, Aztreonam, or Imipenem + Vancomycin, Teicoplanin, or Linezolid	ASM	3H6K
Tornero (2013)	Yes	BAS	Ceftazidime (2 g/8 h) + Vancomycin (1 g/12 h)	10D	Not standardized
Beldman (2021)	Non-systematic	Intravenous antibiotics following local protocol	No detail	2 weeks minimum	3 to 6 months

Intervention – Antibiotic treatment regimen

Different types of the oral antimicrobial regimen were explored. Karlsen et al compared rifampicin 300 mg × 3 orally and cloxacillin 1 g × 4 orally for 4 weeks versus cloxacillin 1 g × 4 orally for 4 weeks after 2 weeks of intravenous treatment. For NRS The network plot (Figure 2.) shows 8 nodes with 13 direct comparisons. All studies explored a combination of Rifampicin-Fluoroquinolones. Only Beldam et al used 3 different Fluoroquinolones: Levofloxacin, Moxifloxacin, Ciprofloxacin. Among all studies, there were 12 other arms exploring oral antimicrobial therapy: 4 combinations with Rifampicin and another agent that fluoroquinolone (Minocycline, Clindamycin, Linezolid, Cotrimoxazole), 2 combinations without Rifampicin and 1 monotherapy with Linezolid alone. Investigated pharmacological interventions against acute staphylococcal PJI are detailed on table 3. Dosage of rifampicin was different between studies, up to 20mg/kg in a divided dose given twice daily with a maximum of 1800mg/D in one study [12]. In more recent studies dosage was 10mg/kg. The most used fluoroquinolone was levofloxacin with the same dosage in all studies that reported it: 500mg/D. For detail of dosages used see appendix 3.

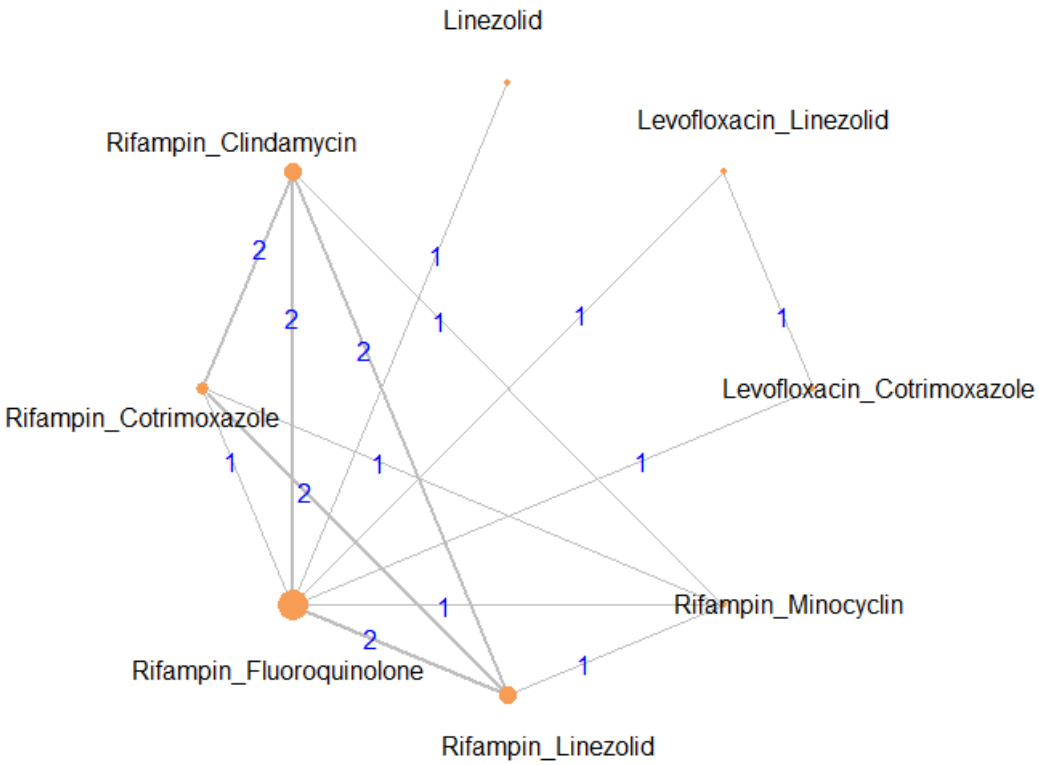


Figure 2. Network of eligible comparisons between treatments used in qualitative analysis**.** *Overall, the network included 405 patients assigned to 8 treatments across 5 trials. Circles (nodes) in the diagrams represent individual treatment; lines between circles represent availability to head-to-head evidence between two treatments, and the number on the lines are the number of trials informing each head-to head comparison.*

Table 3. Remission for oral treatment

Study	Number of patients	Control treatment	Remission	Experimental treatment	Remission	Experimental treatment	Remission	Experimental treatment	Remission
Karlsen (2020)	38	Rifampin_Oxacilline	14/18	Oxacilline	13/20				
Soriano (2006)	18	Rifampin_Levofloxacin	10/11	Rifampin_Clindamycin	5/7				
Vilchez (2010)	45	Rifampin_Levofloxacin	29/33	Rifampin_Clindamycin	3/4	Rifampin_Cotrimoxazole	0/1	Levofloxacin_Cotrimoxazole	2/2
				Rifampin_Linezolid	3/3	Levofloxacin_Linezolid	2/2		
Senneville (2011)	16	Rifampin_Levofloxacin	12/13	Linezolid	3/3				
Tornero (2013)	57	Rifampin_Levofloxacin	40/46	Rifampin_Linezolid	9/11				
Beldman (2021)	269	Rifampin_Levofloxacin	71/81	Rifampin_Ciprofloxacin	36/44	Rifampin_Moxifloxacin	30/34	Rifampin_Clindamycin	25/29
				Rifampin_Linezolid	30/38	Rifampin_Cotrimoxazole	15/24	Rifampin_Minocyclin	15/19
Total	443								

Outcome

Remission was the main outcome for almost all studies except for Beldman which used failure as the main outcome [42]. All studies had a common basis in the definition of remission: the lack of clinical signs and symptoms of PJI, and CRP < 1mg/L except for Senneville et al [12] who did not give value for CRP. But there were additional criteria that were very different. The need for a second debridement within the first days after the first was not considered as a failure by Vilchez et al[40], whereas for others, all re-interventions were considered a failure. The patient who developed a non-septic complication that required prosthesis replacement and cultures of deep tissues negative were not considered failure for Soriano [39] and Tornero [41], whereas it was for all others (for details, see appendix 4). Secondary outcomes that we stated in the protocol (adverse events, adherence to antibiotic regimens during the oral antimicrobial treatment, death, function of the joint with standard scale, quality of life evaluated by a standard scale, development of antibiotic resistance in case of relapsing infection) were not available.

Length of follow-up

Follow-up-time was at least 2 years for all studies [12, 19, 39–41] except for one study which had a follow-up of one year [42]. Nevertheless, Relapse-free survival for patients who received Rifampicin-based therapy was described as up to 500 days and no relapses were seen between 360 days and 500 days.

Quantitative synthesis

The network for efficacy assessment of remission can be seen in figure 3. The network explored 5 different treatments, all based on a combination of Rifampicin with another antibiotic. All drugs had at least one direct comparison with a combination of Rifampicin-Fluoroquinolone. The most compared combination were Rifampicin-Fluoroquinolone vs Rifampicin-Clindamycin (3 studies) followed by Rifampicin-Fluoroquinolone vs Rifampicin-Linezolid (2 studies).

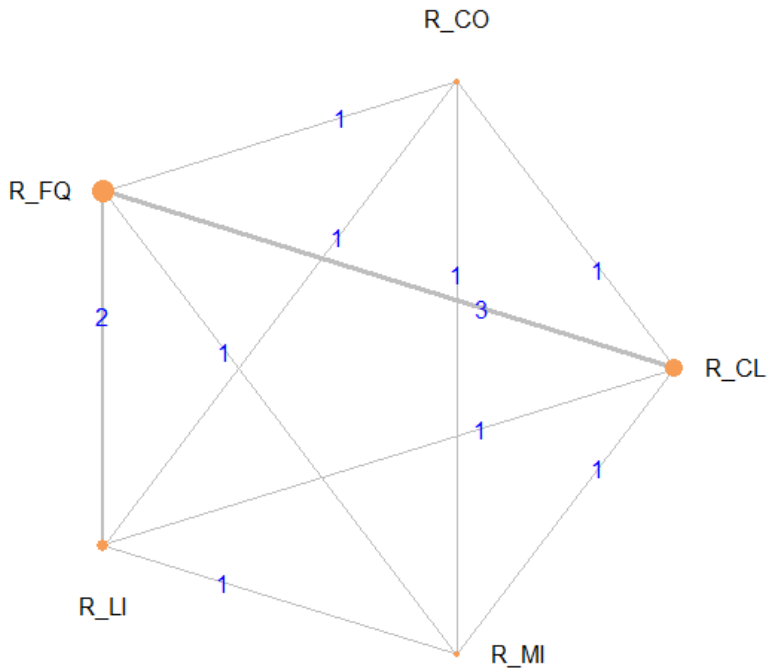


Figure 3. Network of eligible comparisons between treatments used in quantitative analysis**.** *Overall, the network included 381 patients assigned to 5 treatments across 4 trials. (R_FQ: Rifampicin-Fluoroquinolone; R_LI: Rifampicin-Linezolid; R_MI: Rifampicin-Mincocycline; R_CL: Rifampicin-Clindamycin; R_CO: Rifampicin-Cotrimoxazole)*

None of the comparisons reached significance. Rifampicin associated with Fluoroquinolones was the combination with the best RR when compared to other combinations but did not reach significance for any comparison. Rifampicin-Cotrimoxazole seems to be the combination with the lowest remission rate. Rifampicin-Linezolid, Rifampicin-Clindamycin, or Rifampicin-Mincocycline were similar with RR around 1 (figure 4). SUCRA analysis confirmed these results. Combined Rifampicin-Fluoroquinolones (SUCRA 0.79) were at the highest rank followed by Rifampicin-Clindamycin (0.56) or Rifampicin-Linezolid (0.51) or Rifampicin-Minocycline (0.49). Combined Rifampicin-Cotrimoxazole was at the lowest rank in terms of remission (0.14). Figure 5 represents a rank order plot, ranking each regimen by their outcome.

A summary of the pairwise comparisons is shown in appendix 5. There was no heterogeneity. Comparisons of direct versus indirect treatment estimates did not reveal any significant differences. Inconsistency for the entire network meta-analysis for remission was not significant

(p=0.81). As Beldman and colleagues reports the outcome at 1 year, we performed several sensitivity analyses. Each analysis modified the failure rate of a treatment group by adding 5% failure I this group. It didn't change the main results: RR were similar, no one reach significance and the ordering of the treatment was the same. For details see appendix 4.

R_FQ				
1.08 (0.76, 1.90)	**R_CL**			
1.13 (0.61, 2.42)	1.05 (0.50, 2.09)	**R_MI**		
1.10 (0.69, 1.94)	1.02 (0.53, 1.75)	0.97 (0.46, 1.98)	**R_LI**	
1.42 (0.74, 3.12)	1.31 (0.61, 2.68)	1.25 (0.55, 2.80)	1.29 (0.62, 2.76)	**R_CO**

Figure 4. League table of pairwise comparisons in network meta-analysis for attaining a sustained remission. For example, Rifampicin-FQ seems to be better than R-Cotrimoxazole with a RR of 1.42 in favour of remission. *(R_FQ: Rifampicin-Fluoroquinolone; R_LI: Rifampicin-Linezolid; R_MI: Rifampicin-Minocycline; R_CL: Rifampicin-Clindamycin; R_CO: Rifampicin-Cotrimoxazole)*

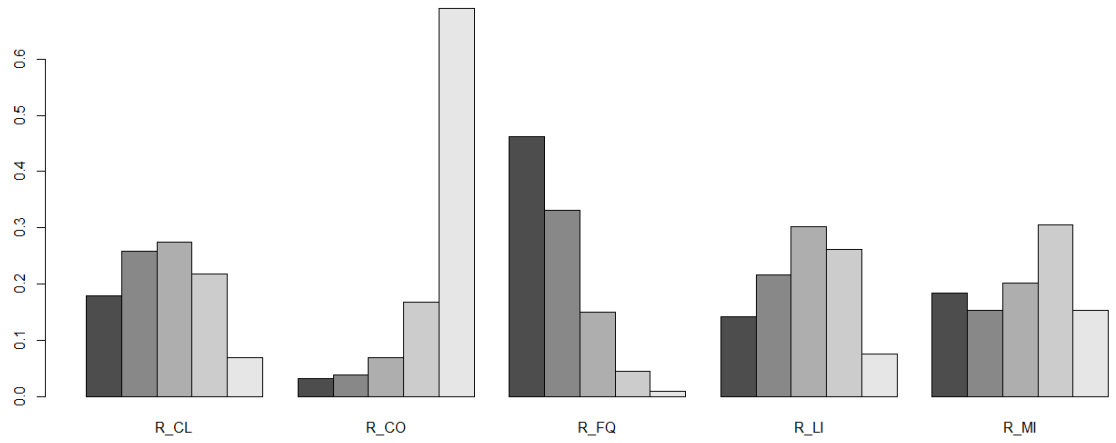


Figure 5. Rank plot applied to the 5 antimicrobial combinations illustrating empirical probabilities that each treatment is ranked first through fifth (left to right) *(R_FQ: Rifampicin-Fluoroquinolone; R_LI: Rifampicin-Linezolid; R_MI: Rifampicin-Minocycline; R_CL: Rifampicin-Clindamycin; R_CO: Rifampicin-Cotrimoxazole)*

Risk of bias in the studies that were included

The only randomized trial had a high risk of bias defined by the “Risk-of-bias tool for randomized trials” (figure 6). 26% of patient dropped out before completion of treatment, authors planned to perform an intention-to-treat analysis, they only performed a per protocol analysis. All NRS studies had critical Risks of Bias defined by the "Risk of Bias in Non-Randomized Studies – of Intervention" (ROBINS-I). All had critical Risks Of Bias (ROB) concerning confounding. Most of the studies were case-control designed to find risk factors of remission vs. failure. They did not report the risk factors of patients according to the treatment they received and did not make any adjustments in their analysis. One study presented an immortal time bias since they included patients who failed before switching to oral treatment in the non-rifampicin group [42]. All studies had serious ROB concerning the measurement of outcomes because outcome measure was subjective and the outcome was assessed by assessors aware of the intervention received by study participants. The majority of the other domains were at a moderate or a low ROB. Figure 7 summarizes the quality assessment by the domain for NRS (details quality of the studies are presented in appendix 5).

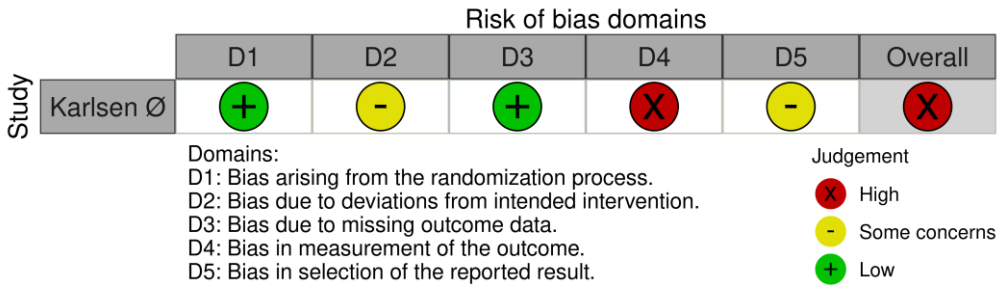


Figure 6. Risk Of Bias 2 in Randomized Studies (RoB2)

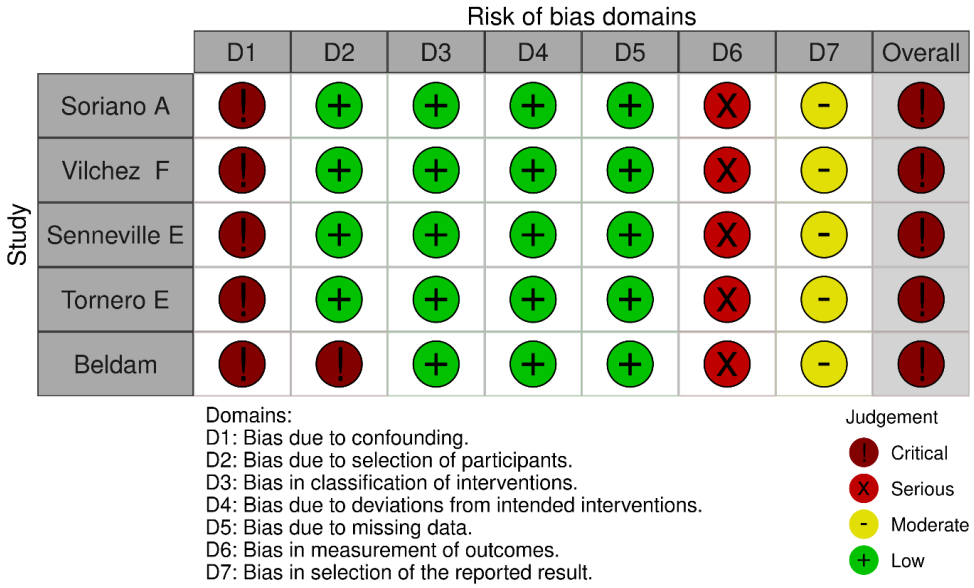


Figure 7. Risk Of Bias in Non-Randomized Studies - of Interventions (ROBINS-I tool)

DISCUSSION

Summary of the main results

Our systematic review and network meta-analysis was conducted to inform clinician using the best literature available. The results confirmed that the literature is scarce on the subject but it seems that the association of Rifampicin and Fluoroquinolone could be the best regimen.

From 2240 references, we only included 6 trials, 1 RCT, and 5 NRS in our systematic review. Papers were mainly excluded due to the high heterogeneity of the population, involving DAIR, but also replacement, osteosynthesis, and arthrodesis. Unfortunately, the raw datasets were no longer available or we did not receive responses from the authors to work on individual patient data.

Working on DAIR excluding another kind of surgical procedure is of interest. When we exchange the prosthesis, in a 1-stage or a 2-stage procedure, biofilm is mechanically eradicated. When a DAIR procedure is performed, the risk of relapse is higher due to the potential bacterial persistence in biofilm at the implant surface when compared to an exchange procedure. In this context, the use antibiotic(s) that target bacterial biofilm is of interest [43, 44]. In contrast to PJI, the management of an osteosynthesis infection can be done with temporary suppressive antibiotic therapy during the consolidation period. Removal of the osteosynthesis after consolidation will remove the biofilm and provide a high probability of eliminating the infection. Management of PJI with an exchange or an osteosynthesis cannot be compared with management of PJI with DAIR [45].

That is the reason why some of the trials that were used for guidelines were not included in the systematic review. For example, IDSA recommendations for acute PJI are mainly based on the RCT of Zimmerli [18]. This study highlights the high successful rate of the Rifampicin-Ciprofloxacine combination regimen when compared to the ciprofloxacin monotherapy. We did not include this article in our NMA because it included two types of infections (osteosynthesis

infection and PJI) and results for PJI were not individualizable. Nevertheless, in this study rifampicin-fluoroquinolone has been compared to monotherapy of ciprofloxacin which was probably not the best comparator to a combination of rifampicin treatment as confirmed by the emergence of staphylococci in the quinolone's monotherapy group (4 of the 5 failures this group were due to ciprofloxacin resistance).

Two systematic reviews and meta-analysis on rifampicin used in prosthetic joint infection [46, 47] have been published recently and assessed the effectiveness of rifampicin in PJI. One failure in the methodology was that they combine RCT and NRS. Moreover, surveys included were heterogeneous and not comparable. In a study published by Scheper [46], they included staphylococcal prosthetic joint infection (PJI) treated by DAIR but they included patients with and without chronic oral suppressive antibiotics, patients with intravenous therapy and with oral therapy. In a study published by Kruse they included patients with different surgical procedures and different of micro-organisms (*Staphylococcus*, *Streptococcus*) [47].

Only one RCT, performed by Karlsen et al [19], met our inclusion criteria. Authors explored compared Rifampicin-Cloxacillin versus monotherapy of Cloxacillin and did not find a significant difference between the two regimens. This article has several limitations that make it difficult to interpret the results. One of the main limits of the study of Karlsen et al is the low number of subjects included. The study is underpowered and thus does not allow any conclusion on the efficacy of the antimicrobial regimen used. The authors aimed to include at least 100 subjects in each group but included only 48 patients, 38 patients for our population of interest. On methicillin-susceptible staphylococci, the success rate with rifampicin combination was 78% (14 out of 18 patients) whereas the monotherapy group led to treatment success in 65% (13 out of 20 patients). By increasing the sample size based on the number of subjects the authors aimed to include, the results would reach statistical significance. Moreover, a combination of rifampicin with oral cloxacillin does not seem to be the most appropriate because cloxacillin has low oral

bioavailability (37%) and poor bone penetration [48]. Other limitations are exposed by Renz et al [26]. The applicability of the results of this study remains uncertain.

We could conduct our NMA on NRS only. Our network meta-analysis showed that the combination of Rifampicin-Fluoroquinolone is the combination that has been the more evaluated and seems to be the most effective but the results did not reach significance. A regimen of rifampicin associated with linezolid or clindamycin or minocycline seems to be similar in terms of clinical outcome. The combination of Rifampicin with cotrimoxazole seems to be the least strategy. These results can be explained because of the bone penetration for these antibiotics [49–54] and the activity again biofilm for rifampicin and linezolid [55, 56]. The sample size for oral antimicrobial therapy without rifampicin was too small and we could not include those data in our NMA. So far, data available in the literature are insufficient to assess the efficacy of a rifampicin-free regimen.

Strength and weakness of the study

We conducted the first networked meta-analysis that looked at oral antibiotic treatment of PJI due Staphylococcus treated by DAIR. The strengths of our study is that we were interested in a specific population and there was no statistical heterogeneity. We conducted a systematic review in accordance with Cochran's recommendations and did not combine RCT and NRS.

One main limitation is that all studies were NRS. Moreover, most of the studies are case-control studies designed to explore predictors of treatment failure in prosthetic joint infections treated with debridement and were not designed to find the best treatment. The reported results are secondary endpoints and the authors did not use adjustment methods to take into account confounding factors but only presented the raw results. As a result, they had a critical risk of bias, and the quality of evidence for these comparisons was graded as very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of the

effect [36]. Moreover, most of evidences were based on one study since the study of Beldman represented 70% of patients included in the NMA (269 of 381 patients).

Another limit is that there were some differences between the population study and the treatment received. To conduct NMA, transitivity need to be evaluate by comparing the distribution of effect modifiers across the different comparisons [20]. Imbalanced distributions would threaten the plausibility of the transitivity assumption and thus the validity of indirect comparison. First, the definition of prosthetic joint infection was slightly different between studies but they were relatively similar and all definitions used the same microbiological criteria. The differences should not have interfered with the estimation of treatment efficiency.

DAIR is indicated for acute prosthetic joint infection, but not all studies had the same definition of acute infection. Most studies included patients with infections occurring during the first month after prosthetic joint implant. Beldman et al included patients with symptoms up to 3 months after prosthesis placement and also included patients with "late acute infection" which means that they had acute symptoms more than 90 days after prosthetic joint implantation. There is still a debate about the time interval from index surgery to DAIR, but it has been suggested that a success rate could be unchanged up to one year after surgery [7]. Most of the studies mixed monomicrobial and polymicrobial infections. The prognosis of these infections were different and a CoNS infection or a polymicrobial infection was described by several studies as a negative prognostic factor [57, 58]. Finally, the definition of failure presented points of divergence between the studies. Some studies considered a second DAIR procedure as a failure, others don’t, and some considered a failure as a new infection with any germ, while others considered failures as reinfection with the same germ and differentiate re-infection with another germ. Even if, there was no statistical inconsistency in our network meta-analysis, these discrepancies may have altered transitivity between studies and could introduce bias.

Author's conclusion

Implications for practice

In conclusion, our systematic review and network meta-analysis found that, to date, a combination of Rifampicin-Fluoroquinolones is the treatment of PJI due to staphylococcus treated by DAIR with the best level of evidence. But this level of evidence is still low. It is difficult to hierarchize other treatments but the combination of rifampicin and cotrimoxazole seems the least appropriate and we should favor the combination of rifampicin with linezolid or clindamycin or cyclin. There is not enough clinical data to recommend a treatment when rifampicin can't be used. The choice can only be made on the pharmacodynamic and pharmacokinetic properties of the antibiotics.

Implications for research

Our networked meta-analysis provides an update on the state of the literature on this topic and emphasizes the need for new quality studies with specific questions to increase the level of evidence in the management of staphylococcal PJI treated by DAIR. We believe it is important to focus future randomized trials on three unresolved issues. Can we use an alternative to rifampicin, such as rifabutin, to decrease adverse effects and increase patient compliance? Can another antibiotic accompany rifampicin to spare fluoroquinolones, and which of the antibiotics most commonly used to date (Doxycycline, Linezolid, Clindamycin) is the most appropriate? Or can we use a combination without rifamycin class antibiotics? To increase the chances of success, we believe that it is crucial to use a combination of antibiotics with good bioavailability and good bone diffusion, in contrast to what was used in the study by Karlsen et al [19]. Randomized clinical trials remain the studies that give the highest level of evidence, but for organizational and economic reasons, they seem difficult and tedious to organize in the treatment of PJI. Therefore, it seems important, while waiting for the constitution of these trials, to carry out observational studies using state of the art methodology (emulated trials).

Supplementary Material

Appendix 1: **Information sources and literature search**

Appendix 2: **Data collection**

Appendix 3: **Antimicrobial regimen and outcomes definition**

Appendix 4: **Pair-wise analysis, consistency and sensitive analysis**

Appendix 5: **Risk of bias assessment**

DISCUSSION de la thèse-article

Nous avons réalisé une revue systématique de la littérature et une méta-analyse en réseau pour apporter aux cliniciens une actualisation et une évaluation de l'état des connaissances. Les résultats mettent en avant que l'association de Rifampicine-Fluoroquinolone pourrait être le meilleur traitement antibiotique oral des infections sur prothèses ostéoarticulaires à staphylocoque. Néanmoins, le niveau de preuve reste faible.

Sur 2240 références, nous n'avons inclus dans la revue systématique que 6 études, 1 essai randomisé, et 5 essais non randomisés. Les articles ont été principalement exclus en raison de la grande hétérogénéité des populations, incluant des infections sur prothèses ostéoarticulaires prises en charges par arthrotomies, synovectomies, lavage, mais également par changement en 1 ou 2 temps ; ainsi que des infections sur matériel d'ostéosynthèses et d'arthrodèses. Malheureusement, les résultats n'étaient pas détaillés par sous-groupes dans les études et nous n'avons pas reçu de réponse des auteurs pour travailler sur les données individuelles des patients. Limiter notre population aux patients pris en charge par arthrotomie, synovectomie, lavage en excluant les autres types de procédures chirurgicales et les infections sur matériel non articulaires est un point essentiel de ce travail. Cette prise en charge n'est pas comparable aux prises en charge réalisant une ablation du matériel tant dans ses indications (patient et donc réussite possible différente) que dans ses implications sur le plan de l'efficacité des stratégies thérapeutiques. En effet, lorsqu'une prothèse est remplacée, dans une procédure en une ou deux étapes, le biofilm est éradiqué mécaniquement. Dans le cadre d'une arthrotomie, synovectomie, lavage, le risque de rechute est plus élevé en raison de la persistance potentielle de bactéries dans le biofilm à la surface de l'implant. Dans ce contexte, l'utilisation d'un ou plusieurs antibiotiques ciblant le biofilm bactérien parait essentiel [43, 44]. De plus, contrairement aux IPOA, la gestion d'une infection de matériel d'ostéosynthèse peut se faire par une antibiothérapie suppressive temporaire pendant la période de consolidation. Le retrait du

matériel d’ostéosynthèse après la consolidation éliminera le biofilm et offrira une forte probabilité d'éliminer l'infection. La prise en charge des IPOA avec changement de prothèse ou des infections de matériel d’ostéosynthèse ne peut pas être comparée à la prise en charge d’IPOA traitées par arthrotomie, synovectomie, lavage [45].

Certains articles majeurs, utilisés pour établir les recommandations n'ont pas pu être inclus dans notre revue systématique car ils incluaient plusieurs populations. Par exemple, les recommandations de l'IDSA pour des IPOA aiguës ont été élaborées en se basant en partie sur l’essais clinique de Zimmerli [18]. Cette étude montre un taux de succès plus élevé du traitement combiné Rifampicine-Ciprofloxacine par rapport à une monothérapie par Ciprofloxacine. Nous n'avons pas inclus cet article dans notre MAR car il incluait deux types d'infections (infection sur matériel d’ostéosynthèse et IPOA). De plus, dans cette étude, la combinaison Rifampicine-Fluoroquinolone a été comparée à la monothérapie de ciprofloxacine qui n'était, probablement, pas le meilleur comparateur comme le confirme l'émergence de résistances aux fluoroquinolones dans le groupe monothérapie ciprofloxacine (4 des 5 échecs de ce groupe étaient dus à une résistance à la ciprofloxacine).

2 revues systématiques et méta-analyses sur l’utilisation de la rifampicine dans le traitement des IPOA ont été récemment publiées [46, 47]. L'un des défauts méthodologiques de ces études est qu'elles combinaient des essais cliniques randomisés et non randomisés. De plus, les études inclues étaient très hétérogènes en termes de populations et de prise en charge. Dans l’étude publiée par Scheper [46], les auteurs ont inclus des IPOA à staphylocoque traitées par arthrotomie, synovectomie, lavage, mais ils ont comparé des patients avec des antibiothérapies orales suppressives et d’autres patients sans ; des patients avec une antibiothérapie par voie intraveineuse et des patients avec une antibiothérapie par voie orale. Dans l’étude publiée par Kruse [47], différentes procédures chirurgicales ont été inclues, ainsi que différents micro-organismes (staphylocoques, streptocoques) [37].

Un seul essai randomisé, publié en 2020 [19] répondait à nos critères d'inclusion. Les auteurs

ont comparé Rifampicine-Cloxacilline à une monothérapie de Cloxacilline et n'ont pas trouvé de différence significative entre les deux traitements. Cet article présente cependant plusieurs limites qui rendent complexe l'interprétation des résultats. L'une des principales limites de cette étude est le faible nombre de sujets inclus. L'étude manque de puissance et ne permet donc pas de conclure à la supériorité d'un des deux traitements. Les auteurs avaient pour objectif d'inclure au moins 100 sujets dans chaque groupe mais n'ont inclus que 48 patients, et 38 patients pour notre population d'intérêt. En ce qui concerne la population incluse dans la revue systématique, le taux de succès avec l'association Rifampicine-Cloxacilline était de 78% (14 patients sur 18) contre 65% pour le groupe monothérapie (13 patients sur 20). En augmentant la taille de l'échantillon en fonction du nombre de sujets que les auteurs souhaitaient inclure, les résultats seraient statistiquement significatifs en faveur de la combinaison Rifampicine-Cloxacilline. Enfin la cloxacilline a une faible biodisponibilité orale (37%) et une faible diffusion osseuse [38], les propriétés de cet antibiotique ne sont pas optimales pour le traitement oral des IPOA. D'autres limites sont exposées par Renz et al [26].

Nous n'avons pu réaliser notre MAR que sur les essais cliniques non randomisés et comparer 4 traitements. L'association Rifampicine-Fluoroquinolone est la combinaison qui a été la plus testée et qui semble être la plus efficace, mais les résultats ne sont pas significatifs. L'association Rifampicine-Cotrimoxazole est celle qui semble la moins efficace. Les trois autres combinaisons présentent une efficacité similaire. Ces résultats peuvent s'expliquer par une bonne diffusion osseuse pour ces antibiotiques [49–54] et par l'activité anti-biofilm de la rifampicine et du linézolide [55, 56]. Les effectifs évaluant des traitements sans rifampicine étaient trop faibles pour être inclus dans notre MAR. Les données disponibles dans la littérature sont donc insuffisantes pour évaluer l'efficacité d'un traitement antibiotique sans rifampicine.

Forces et limites de l'étude

Nous avons réalisé la première MAR sur les traitements antimicrobiens oraux des infections sur prothèses ostéoarticulaires. De plus, nous nous sommes intéressés à une population spécifique

pour maximiser l'hypothèse de transitivité des MAR. Cela se traduit par une absence d'hétérogénéité statistique dans nos résultats.

Une limite majeure de notre MAR est que toutes les études inclues étaient des essais non randomisés. De plus, la plupart des études sont des études cas-témoins conçues pour explorer les facteurs pronostics d'échec du traitement des IPOA et n'ont pas été conçues pour trouver le meilleur traitement. Les résultats que nous avons utilisés ont été rapportés sans méthode d'ajustement pour prendre en compte les facteurs de confusion. Par conséquent, cela représente un risque de biais majeur et l'effet réel des traitements est donc susceptible d'être différent des estimations présentées. De plus, la plupart des données sont extraites d'une seule étude puisque l'étude de Beldman représente 68% des patients inclus dans l'AMN (269 sur 392 patients).

Une autre limite est qu'il existait des différences entre les études en termes de populations inclues et les prises en charge des patients (en dehors de l'intervention que nous avons évaluée). Premièrement, la prise en charge par arthrotomie synovectomie lavage est indiquée pour les infections « aiguës » de prothèses ostéoarticulaires, mais toutes les études n'ont pas la même définition de l'infection « aiguë ». La plupart des études ont inclus des patients présentant des infections survenant au cours du premier mois suivant l'implantation de la prothèse articulaire. Mais certaines études, comme celle de Beldman, ont inclus des patients présentant des symptômes plus tardivement, jusqu'à 3 mois après la mise en place de la prothèse. L'intervalle de temps entre la mise en place de la prothèse et la prise en charge chirurgicale de l'infection fait toujours l'objet d'un débat, mais des auteurs ont récemment publié que le taux de réussite pouvait être similaire jusqu'à un an après la chirurgie [7]. La plupart des études ont mélangé les infections mono-microbiennes et polymicrobiennes. Le pronostic de ces infections est différent et une infection à staphylocoques à coagulase négative ou une infection polymicrobienne est décrite par plusieurs études comme un facteur pronostique péjoratif [57, 59]. Enfin, la définition de l'échec présente des points de divergence entre les études. Certaines

études considèrent qu'une deuxième procédure de lavage était un échec, d'autres non. De plus certaines études considèrent un échec comme une nouvelle infection avec n'importe quel pathogène, tandis que d'autres considèrent les échecs comme une réinfection avec le même pathogène et différencient la réinfection avec un autre pathogène. Pour réaliser une MAR, les auteurs doivent évaluer la transitivité en comparant la distribution des facteurs susceptibles de modifier l'effet des traitements entre les études [20]. Des déséquilibres menaceraient l'hypothèse de transitivité et donc la validité des comparaisons indirectes. Néanmoins, les divergences que nous avons constatées sont limitées et ne remettent pas en cause l'hypothèse de transitivé.

Conclusion des auteurs

Implications pour la pratique

En conclusion, notre revue systématique et notre méta-analyse en réseau ont montré qu'à ce jour, dans le cadre d'une prise en charge des IPOA à staphylocoque par une procédure « arthrotomie, synovectomie, lavage », l'association Rifampicine-Fluoroquinolone est le traitement qui présente le meilleur niveau de preuve et qui semble être le plus efficace. Mais ce niveau de preuve est encore faible. Il est difficile de hiérarchiser les autres traitements. D'après nos résultats, l'association rifampicine et cotrimoxazole semble la moins appropriée et les associations rifampicine avec linézolide ou clindamycine ou cycline semblent à privilégier. Il n'y a pas assez de données cliniques pour recommander un traitement lorsque la rifampicine ne peut pas être utilisée. Le choix ne peut se faire qu'en fonction des propriétés pharmacodynamiques et pharmacocinétiques des antibiotiques.

Implications pour la recherche

Notre méta-analyse en réseau fournit une mise à jour de la littérature sur ce sujet et souligne le besoin de nouvelles études de qualité avec des questions spécifiques pour augmenter le niveau de preuve dans la gestion des IPOA à staphylocoque traitées par arthrotomie, synovectomie,

lavage. Nous pensons qu'il est important d'axer les futurs essais randomisés sur trois questions non résolues. Peut-on utiliser une alternative à la rifampicine, comme la rifabutine, pour diminuer les effets indésirables et augmenter l'observance du traitement par le patient ? Un autre antibiotique peut-il accompagner la rifampicine pour épargner les fluoroquinolones, et lequel des antibiotiques les plus utilisés à ce jour (Cycline, Linézolide, Clindamycine) est le plus approprié ? Ou pouvons-nous utiliser une combinaison sans antibiotique de la classe des rifamycines ? Pour augmenter les chances de succès, nous pensons qu'il est crucial d'utiliser une combinaison d'antibiotiques avec une bonne biodisponibilité et une bonne diffusion osseuse, contrairement à ce qui a été utilisé dans l'étude de Karlsen et al [19]. Les essais cliniques randomisés restent les études qui donnent le plus haut niveau de preuve, mais qui pour des raisons organisationnelles et économiques, sont difficiles à mener dans le traitement de l'IPOA. Il semble donc important, en attendant la constitution de ces essais, de réaliser des études observationnelles répondant à notre question de recherche et utilisant les méthodes actuelles d'ajustement sur les facteurs de confusion avec la réalisation d’essais émulés portant sur des groupes de patients homogènes tant dans leur histoire clinique que dans leur prise en charge médico-chirurgicale.

BIBLIOGRAPHIE

1. Wang F-D, Wang Y-P, Chen C-F, Chen H-P. The incidence rate, trend and microbiological aetiology of prosthetic joint infection after total knee arthroplasty: A 13 years' experience from a tertiary medical center in Taiwan. J Microbiol Immunol Infect Wei Mian Yu Gan Ran Za Zhi. 2018;51:717–22.

2. Koh CK, Zeng I, Ravi S, Zhu M, Vince KG, Young SW. Periprosthetic Joint Infection Is the Main Cause of Failure for Modern Knee Arthroplasty: An Analysis of 11,134 Knees. Clin Orthop. 2017;475:2194–201.

3. Kurtz S, Ong K, Lau E, Mowat F, Halpern M. Projections of primary and revision hip and knee arthroplasty in the United States from 2005 to 2030. J Bone Joint Surg Am. 2007;89:780–5.

4. Sculco TP. The economic impact of infected joint arthroplasty. Orthopedics. 1995;18:871–3.

5. 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 Off Publ Infect Dis Soc Am. 2013;56:e1–25.

6. Prothèse de hanche ou de genou : diagnostic et prise en charge de l'infection dans le mois suivant l'implantation. 2014;:134.

7. Löwik CAM, Parvizi J, Jutte PC, Zijlstra WP, Knobben BAS, Xu C, et al. Debridement, antibiotics, and implant retention is a viable treatment option for early periprosthetic joint infection presenting more than 4 weeks after index arthroplasty. Clin Infect Dis. 2020;71:630–6.

8. Cara A, Ballet M, Hemery C, Ferry T, Laurent F, Josse J. Antibiotics in Bone Cements Used for Prosthesis Fixation: An Efficient Way to Prevent Staphylococcus aureus and Staphylococcus epidermidis Prosthetic Joint Infection. Front Med. 2020;7:576231.

9. Berberich CE, Josse J, Laurent F, Ferry T. Dual antibiotic loaded bone cement in patients at high infection risks in arthroplasty: Rationale of use for prophylaxis and scientific evidence. World J Orthop. 2021;12:119–28.

10. Mulazimoglu L, Drenning SD, Muder RR. Vancomycin-gentamicin synergism revisited: effect of gentamicin susceptibility of methicillin-resistant Staphylococcus aureus. Antimicrob Agents Chemother. 1996;40:1534–5.

11. Cara A, Ferry T, Laurent F, Josse J. Prophylactic Antibiofilm Activity of Antibiotic-Loaded Bone Cements against Gram-Negative Bacteria. Antibiot Basel Switz. 2022;11:137.

12. Senneville E, Joulie D, Legout L, Valette M, Dezèque H, Beltrand E, et al. Outcome and predictors of treatment failure in total hip/knee prosthetic joint infections due to Staphylococcus aureus. Clin Infect Dis Off Publ Infect Dis Soc Am. 2011;53:334–40.

13. Trampuz A, Zimmerli W. New strategies for the treatment of infections associated with prosthetic joints. Curr Opin Investig Drugs Lond Engl 2000. 2005;6:185–90.

14. Fisman DN, Reilly DT, Karchmer AW, Goldie SJ. Clinical effectiveness and cost-effectiveness of 2 management strategies for infected total hip arthroplasty in the elderly. Clin Infect Dis Off Publ Infect Dis Soc Am. 2001;32:419–30.

15. Moran E, Masters S, Berendt AR, McLardy-Smith P, Byren I, Atkins BL. Guiding empirical antibiotic therapy in orthopaedics: The microbiology of prosthetic joint infection managed by debridement, irrigation and prosthesis retention. J Infect. 2007;55:1–7.

16. Li H-K, Rombach I, Zambellas R, Walker AS, McNally MA, Atkins BL, et al. Oral versus Intravenous Antibiotics for Bone and Joint Infection. N Engl J Med. 2019;380:425–36.

17. Bernard L, Arvieux C, Brunschweiler B, Touchais S, Ansart S, Bru J-P, et al. Antibiotic Therapy for 6 or 12 Weeks for Prosthetic Joint Infection. N Engl J Med. 2021;384:1991–2001.

18. 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;279:1537–41.

19. Karlsen ØE, Borgen P, Bragnes B, Figved W, Grøgaard B, Rydinge J, et al. Rifampin combination therapy in staphylococcal prosthetic joint infections: a randomized controlled trial. J Orthop Surg. 2020;15:365.

20. Salanti G. Indirect and mixed-treatment comparison, network, or multiple-treatments meta-analysis: many names, many benefits, many concerns for the next generation evidence synthesis tool. Res Synth Methods. 2012;3:80–97.

21. Cochrane Handbook for Systematic Reviews of Interventions. /handbook. Accessed 17 Jun 2021.

22. Zimmerli W, Trampuz A, Ochsner PE. Prosthetic-Joint Infections. N Engl J Med. 2004;351:1645–54.

23. McDonald DJ, Fitzgerald RH, Ilstrup DM. Two-stage reconstruction of a total hip arthroplasty because of infection. J Bone Joint Surg Am. 1989;71:828–34.

24. Tsukayama DT, Estrada R, Gustilo RB. Infection after total hip arthroplasty. A study of the treatment of one hundred and six infections. J Bone Joint Surg Am. 1996;78:512–23.

25. Stefánsdóttir A, Johansson D, Knutson K, Lidgren L, Robertsson O. Microbiology of the infected knee arthroplasty: report from the Swedish Knee Arthroplasty Register on 426 surgically revised cases. Scand J Infect Dis. 2009;41:831–40.

26. Renz N, Trampuz A, Zimmerli W. Controversy about the Role of Rifampin in Biofilm Infections: Is It Justified? Antibiot Basel Switz. 2021;10.

27. Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. BMJ. 2015;350:g7647.

28. Stone PW. Popping the (PICO) question in research and evidence-based practice. Appl Nurs Res ANR. 2002;15:197–8.

29. Grey Matters: a practical tool for searching health-related grey literature | CADTH. https://www.cadth.ca/resources/finding-evidence/grey-matters. Accessed 17 Jun 2021.

30. Sterne JA, Hernán MA, Reeves BC, Savović J, Berkman ND, Viswanathan M, et al. ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. BMJ. 2016;355:i4919.

31. DerSimonian R, Laird N. Meta-analysis in clinical trials. Control Clin Trials. 1986;7:177–88.

32. Lu G, Ades AE. Combination of direct and indirect evidence in mixed treatment comparisons. Stat Med. 2004;23:3105–24.

33. Valkenhoef G van, Dias S, Ades AE, Welton NJ. Automated generation of node-splitting models for assessment of inconsistency in network meta-analysis. Res Synth Methods. 2016;7:80–93.

34. Salanti G, Ades AE, Ioannidis JPA. Graphical methods and numerical summaries for presenting results from multiple-treatment meta-analysis: an overview and tutorial. J Clin Epidemiol. 2011;64:163–71.

35. Guyatt GH, Oxman AD, Kunz R, Brozek J, Alonso-Coello P, Rind D, et al. GRADE guidelines 6. Rating the quality of evidence--imprecision. J Clin Epidemiol. 2011;64:1283–93.

36. Puhan MA, Schünemann HJ, Murad MH, Li T, Brignardello-Petersen R, Singh JA, et al. A GRADE Working Group approach for rating the quality of treatment effect estimates from network meta-analysis. BMJ. 2014;349:g5630.

37. NCT04672525. Rifabutin Versus Rifampicin for Treatment of Staphylococcal PJI Treated With DAIR. https://clinicaltrials.gov/show/NCT04672525. 2020.

38. Moher D, Liberati A, Tetzlaff J, Altman DG, PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Med. 2009;6:e1000097.

39. Soriano A, García S, Bori G, Almela M, Gallart X, Macule F, et al. Treatment of acute post-surgical infection of joint arthroplasty. Clin Microbiol Infect. 2006;12:930–3.

40. Vilchez F, Martínez-Pastor JC, García-Ramiro S, Bori G, Maculé F, Sierra J, et al. Outcome and predictors of treatment failure in early post-surgical prosthetic joint infections due to Staphylococcus aureus treated with debridement. Clin Microbiol Infect Off Publ Eur Soc Clin Microbiol Infect Dis. 2011;17:439–44.

41. Tornero E, Morata L, Martínez-Pastor JC, Bori G, Mensa J, Soriano A. Prosthetic joint infections due to

methicillin-resistant and methicillin-susceptible staphylococci treated with open debridement and retention of the prosthesis. Rev Esp Quimioter. 2013;26:353–9.

42. Beldman M, Löwik C, Soriano A, Albiach L, Zijlstra WP, Knobben BAS, et al. If, when, and how to use rifampin in acute staphylococcal periprosthetic joint infections, a multicentre observational study. Clin Infect Dis Off Publ Infect Dis Soc Am. 2021; (Beldman M.; Löwik C.; Jutte P.) Department of Orthopaedic Surgery, University of Groningen, University Medical Center Groningen, Netherlands. https://doi.org/10.1093/cid/ciab426.

43. Ferry T, Batailler C, Brosset S, Kolenda C, Goutelle S, Sappey-Marinier E, et al. Medical innovations to maintain the function in patients with chronic PJI for whom explantation is not desirable: a pathophysiology-, multidisciplinary-, and experience-based approach. SICOT-J. 2020;6:26.

44. Costerton JW, Stewart PS, Greenberg EP. Bacterial biofilms: a common cause of persistent infections. Science. 1999;284:1318–22.

45. Metsemakers WJ, Kuehl R, Moriarty TF, Richards RG, Verhofstad MHJ, Borens O, et al. Infection after fracture fixation: Current surgical and microbiological concepts. Injury. 2018;49:511–22.

46. Scheper H, Gerritsen LM, Pijls BG, Van Asten SA, Visser LG, De Boer MGJ. Outcome of Debridement, Antibiotics, and Implant Retention for Staphylococcal Hip and Knee Prosthetic Joint Infections, Focused on Rifampicin Use: A Systematic Review and Meta-Analysis. Open Forum Infect Dis. 2021;8:ofab298.

47. Kruse CC, Ekhtiari S, Oral I, Selznick A, Mundi R, Chaudhry H, et al. The Use of Rifampin in Total Joint Arthroplasty: A Systematic Review and Meta-Analysis of Comparative Studies. J Arthroplasty. 2022;:S0883-5403(22)00374-6.

48. Nauta EH, Mattie H. Dicloxacillin and cloxacillin: pharmacokinetics in healthy and hemodialysis subjects. Clin Pharmacol Ther. 1976;20:98–108.

49. Bart G, Zeller V, Kerroumi Y, Heym B, Meyssonnier V, Desplaces N, et al. Minocycline Combined with Vancomycin for the Treatment of Methicillin-Resistant Coagulase-Negative Staphylococcal Prosthetic Joint Infection Managed with Exchange Arthroplasty. J Bone Jt Infect. 2020;5:110–7.

50. Wen S, Zhang T, Yu X, Dong W, Lan T, Fan J, et al. Bone penetration of linezolid in osteoarticular tuberculosis patients of China. Int J Infect Dis IJID Off Publ Int Soc Infect Dis. 2021;103:364–9.

51. Norden CW, Shinners E, Niederriter K. Clindamycin treatment of experimental chronic osteomyelitis due to Staphylococcus aureus. J Infect Dis. 1986;153:956–9.

52. Rimmelé T, Boselli E, Breilh D, Djabarouti S, Bel JC, Guyot R, et al. Diffusion of levofloxacin into bone and synovial tissues. J Antimicrob Chemother. 2004;53:533–5.

53. Kropec A, Daschner FD. Penetration into tissues of various drugs active against gram-positive bacteria. J Antimicrob Chemother. 1991;27 Suppl B:9–15.

54. Goetz J, Keyssner V, Hanses F, Greimel F, Leiß F, Schwarz T, et al. Animal experimental investigation on the efficacy of antibiotic therapy with linezolid, vancomycin, cotrimoxazole, and rifampin in treatment of periprosthetic knee joint infections by MRSA. Bone Jt Res. 2022;11:143–51.

55. Jacqueline C, Caillon J. Impact of bacterial biofilm on the treatment of prosthetic joint infections. J Antimicrob Chemother. 2014;69 Suppl 1:i37-40.

56. Raad I, Hanna H, Jiang Y, Dvorak T, Reitzel R, Chaiban G, et al. Comparative activities of daptomycin, linezolid, and tigecycline against catheter-related methicillin-resistant Staphylococcus bacteremic isolates embedded in biofilm. Antimicrob Agents Chemother. 2007;51:1656–60.

57. Berbari EF, Osmon DR, Duffy MCT, Harmssen RNW, Mandrekar JN, Hanssen AD, et al. Outcome of prosthetic joint infection in patients with rheumatoid arthritis: the impact of medical and surgical therapy in 200 episodes. Clin Infect Dis Off Publ Infect Dis Soc Am. 2006;42:216–23.

58. Lora-Tamayo J, Murillo O, Iribarren JA, Soriano A, Sánchez-Somolinos M, Baraia-Etxaburu JM, et al. A Large Multicenter Study of Methicillin–Susceptible and Methicillin–Resistant Staphylococcus aureus Prosthetic Joint Infections Managed With Implant Retention. Clin Infect Dis. 2013;56:182–94.

59. Lora-Tamayo J, Euba G, Ribera A, Murillo O, Pedrero S, García-Somoza D, et al. Infected hip hemiarthroplasties and total hip arthroplasties: Differential findings and prognosis. J Infect. 2013;67:536–44.

ANNEXES

APPENDIX 1 - Search algorithms

Summary:

Algorithms 1: PubMed search algorithm

Population:

#1 “Prosthesis-Related Infections”[mh]
#2 "Prosthetic Joint Infection*"[tiab]
#3 "Prosthesis-Related Infection*"[tiab]
#4 "Periprosthetic joint infection*"[tiab]
#5 “Arthroplasty infection”[tiab]
#6 “PJI”[tiab]
#7 #1 OR #2 OR #3 OR #4 OR #5 OR #6
#8 “Joint Prosthesis"[mh]
#9 “Arthroplasty, Replacement “ [mh]
#10 “Orthopedic implant”[tiab]
#11 #8 OR #9 OR #10
#12 Periprosthe*[tiab]
#13 Prosthes*[tiab]
#14 Joint[mh]
#15 Joint*[tiab]
#16 knee*[tiab]
#17 shoulder*[tiab]
#18 elbow*[tiab]
#19 hip[tiab]
#20 hips[tiab]
#21 (#12OR #13) AND (#14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20)
#22 infection [mh]
#23 infection* [tiab]
#24 infected [tiab]
#25 #22 OR #23 OR #24
#26 (#11 OR #21) AND #25
#27 Acute[tiab]
#28 Hematogenous[tiab]
#29 Debridement[mh]
#30 Debridement[tiab]
#31 Retention[tiab]
#32 DAIR[tiab]
#33 #27 OR #28 OR #29 OR #30 OR #31 OR #32
#34 (#7 OR 26) AND #33

Intervention:

#35 “Anti-Bacterial Agents”[mh]
#36 Antibiotic*[tiab]
#37 Antistaphylococcal[tiab]
#38 Antimicrobial[tiab]
#39 (rifampin[tiab] or rifampicin[tiab] or rifabutin[tiab] or rifamycins[tiab] or linezolid[tiab] or doxycycline[tiab] or minocycline[tiab] or clindamycin[tiab] or cotrimoxazole[tiab] or fluoroquinolon[tiab] or levofloxacin[tiab] or ciprofloxacin[tiab])
#40 #35 OR #36 OR #37 OR #38 OR #39

Publication

#41 Case Reports[pt]
#42 Meta-Analysis[pt]
#43 Systematic Review[pt]
#44 Review[pt]
#45 #41 OR #42 OR #43 OR #44

#46 (#34 AND #40) NOT #45

Algorithm 2: EMBASE search algorithm

Population:

#1 “Prosthesis infection”;exp
#2 "Prosthetic Joint Infection*";ab,ti
#3 "Prosthesis-Related Infection*";ab,ti
#4 "Periprosthetic joint infection*";ab,ti
#5 “Arthroplasty infection”;ab,ti
#6 “PJI”;ab,ti
#7 #1 OR #2 OR #3 OR #4 OR #5 OR #6
#8 “joint Prosthesis";exp
#9 “Replacement Arthroplasty“;exp
#10 “Orthopedic implant”;ab,ti
#11 #8 OR #9 OR #10
#12 "Periprosthe*";ab,ti
#13 "Prosthes*";ab,ti
#14 "Joint";exp
#15 "Joint*";ab,ti
#16 "Knee*";ab,ti
#17 "Shoulder*";ab,ti
#18 "Elbow*";ab,ti
#19 "Hip";ab,ti
#20 "Hips";ab,ti
#21 (#12OR #13) AND (#14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20)
#22 "Infection";exp
#23 "Infection*";ab,ti
#24 "Infected";ab,ti
#25 #22 OR #23 OR #24
#26 (#11 OR #21) AND #25
#27 "Acute";ab,ti
#28 "Hematogenous";ab,ti
#29 “Debridement";exp
#30 "Debridement";ab,ti
#31 "Retention";ab,ti
#32 "DAIR";ab,ti
#33 #27 OR #28 OR #29 OR #30 OR #31 OR #32
#34 (#7 OR 26) AND #33

Intervention:

#35 "Antiinfective agent";exp
#36 "Antibiotic*";ab,ti
#37 "Antistaphylococcal";ab,ti
#38 "Antimicrobial;ab,ti
#39 ("rifampin";ab,ti or "rifampicin";ab,ti or "rifabutin";ab,ti or "rifamycins";ab,ti or "linezolid";ab,ti or "doxycycline";ab,ti or "minocycline";ab,ti or "clindamycin";ab,ti or "cotrimoxazole";ab,ti or "fluoroquinolon";ab,ti or "levofloxacin";ab,ti or "ciprofloxacin";ab,ti)
#40 #35 OR #36 OR #37 OR #38 OR #39

Publication

#41 "Case Reports";pt
#42 "Meta-Analysis";pt
#43 "SystematicReview";pt
#44 "Review";pt
#45 #41 OR #42 OR #43 OR #44

#46 (#34 AND #40) NOT #45

Algorithm 3: CENTRAL search algorithm

Population:

#1 (Prosthesis-Related Infections):ti,ab,kw
#2 (Prosthetic Joint Infection*):ti,ab,kw
#3 (Prosthesis-Related Infection*):ti,ab,kw
#4 (Periprosthetic joint infection*):ti,ab,kw
#5 (Arthroplasty infection):ti,ab,kw
#6 (PJI):ti,ab,kw
#7 #1 OR #2 OR #3 OR #4 OR #5 OR #6
#8 (joint Prosthesis):ti,ab,kw
#9 (Replacement Arthroplasty):ti,ab,kw
#10 (Orthopedic implant):ti,ab,kw
#11 #8 OR #9 OR #10
#12 (Periprosthe*):ti,ab,kw
#13 (Prosthes*):ti,ab,kw
#14 (Joint):ti,ab,kw
#15 (Joint*):ti,ab,kw
#16 (Knee*):ti,ab,kw
#17 (Shoulder*):ti,ab,kw
#18 (Elbow*):ti,ab,kw
#19 (Hip):ti,ab,kw
#20 (Hips):ti,ab,kw
#21 (#12OR #13) AND (#14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20)
#22 (Infection):ti,ab,kw
#23 (Infection*):ti,ab,kw
#24 (Infected):ti,ab,kw
#25 #22 OR #23 OR #24
#26 (#11 OR #21) AND #25
#27 (Acute):ti,ab,kw
#28 (Hematogenous):ti,ab,kw
#29 (Debridement):ti,ab,kw
#30 (Debridement):ti,ab,kw
#31 (Retention):ti,ab,kw
#32 (DAIR):ti,ab,kw
#33 #27 OR #28 OR #29 OR #30 OR #31 OR #32
#34 (#7 OR 26) AND #33

Intervention:

#35 (Anti-Bacterial Agents):ti,ab,kw
#36 (Antibiotic*):ti,ab,kw
#37 (Antistaphylococcal):ti,ab,kw
#38 (Antimicrobial):ti,ab,kw
#39 ((rifampin):ti,ab,kw or (rifampicin):ti,ab,kw or (rifabutin):ti,ab,kw or (rifamycins):ti,ab,kw or (linezolid):ti,ab,kw or (doxycycline):ti,ab,kw or (minocycline):ti,ab,kw or (clindamycin):ti,ab,kw or (cotrimoxazole):ti,ab,kw or (fluoroquinolon):ti,ab,kw or (levofloxacin):ti,ab,kw or (ciprofloxacin):ti,ab,kw)
#40 #35 OR #36 OR #37 OR #38 OR #39

#41 #34 AND #40

APPENDIX 2 – Data extraction form

GENERAL CHARACTERISTICS

Date of publication (yyyy): |_||_||_||_|

Journal: …….

Title: ……

First author: ……..

Contact (email or address): ……..

Language: ……

Countries: ……

Design study: ☐ Randomized Controlled Trial (RCT) ☐Observational prospective (OP)
☐ Observational retrospective (OR)

If observational: ☐ Cohort ☐ Case control ☐ NA

If RCT:

- Design: ☐superiority trial ☐non-inferiority trial ☐ Equivalence ☐ Not reported ☐ NA

- Blinding: ☐ Open Label ☐ Single Blind ☐ Double blind ☐ Not reported ☐ NA

Centre: ☐ single-centre study ☐ Multicentre study ☐ Not reported

If multicentre study, number of centres: |_||_||_|

Period of recruitment (yyyy): |_||_||_||_|/|_||_||_||_|

POPULATION CHARACTERISTICS

Main inclusion criteria:

Definition of Prosthetic Joint Infection:

☐ EBJIS 2021 ☐ ICM 2018 ☐ ICM 2013 ☐ IDSA 2013 ☐ MSIS 2011

☐ Other: ……

Location of the prosthesis: ☐ Hip(H) ☐ Knee(K) ☐ Shoulder(S) ☐ Hip & Knee (HK)
☐ Hip, Knee and Shoulder (HKS)
☐Other: …….

Microbiology: ☐ Monomicrobial infection (M)

☐ Monomicrobial infection or Polymicrobial infection (MP)

Staphylococci: ☐ *Staphylococcus aureus* (SA)

☐ Coagulase-negative staphylococci (CoNS)

☐ *Staphylococcus aureus* AND Coagulase-negative staphylococci (SA AND CoNS)

☐ Not reported

Characteristics of *Staphylococcus aureus:*

☐ SAMS

☐ SARM

☐ SAMS & SARM

☐ Not reported

☐ NA

Characteristics of coagulase-negative staphylococci:

☐ CoNS MS

☐ CoNS RM

☐ CoNS MS & RM

☐ Not reported

☐ NA

Definition of acute (DOA):

☐ Acute post-operative (<30 days after surgery) (APO)

☐ Late acute (symptoms ≤ 3 weeks and occurring ≥ 3 months after arthroplasty) (LA)

☐ Early onset (<3 months after surgery) (EO)

☐ APO & LA

☐ Other DOA: ……

Intervention DAIR:

☐ Change of modular component (CPM)

☐ Not change of modular component (NotCPM)

☐ Not the same procedure for all patients (CPM/NotCPM)

☐ Not Reported

Empirical antibiotic treatment:

☐ Broad spectrum of B-lactam agent and agent active against SARM (BAS)

☐ Broad spectrum without detail (BWD)

☐ Not Reported

Details of empirical antibiotic treatment: ……

Time to switch to oral:

☐ As soon as results of the preoperative sample culture were available (ASM)

☐ 10 Days (10D)

☐ 1week (1W)

☐ 2week (2W)

☐ Not standardized

☐ Not reported

☐Other: ……

Total duration of treatment: ☐ 3 months for Hip, 6 months for knee (3H/6K) ☐ 3months (3M) ☐ 6weeks (6W) ☐ Not standardized ☐ Not reported ☐Other: ……

Other important inclusion criteria: ……

Main exclusion criteria:

Multiple relapse: ☐ No ☐ Yes ☐ Not reported

Other important exclusion criteria: …….

OUTCOME

Main outcome with definition of the article:

☐Remission:

☐Failure:

☐Other:

Remission outcome(s): ……

Failure outcome(s): ……

Other important information on outcome(s): ……

Follow up:

☐ 1 year (1Y)

☐ 2 years (2Y)

☐ Not reported

☐ Other: ……

STATISTICAL ANALYSIS

For RCT :

Analysis (according to the authors): ☐ Not reported ☐ ITT ☐ ITTm ☐ Per Protocol ☐ NA

Planned sample size: |_||_||_||_| ☐ NA

Beta risk (%): |_||_| ☐ NA

Alpha risk (%): |_||_| ☐ NA

CONTROL INTERVENTION

Treatment in the control arm

Control:

☐No treatment ☐Oral antibiotic treatment (OAT)

Oral antibiotic treatment: ☐ Monotherapy ☐ Dual therapy

If Dual therapy: ☐ Rifampin and Fluoroquinolones (FQ)

☐ Rifampin combination without FQ

☐ Combination without Rifampin

☐ Other: ……

Detail ATB1: ☐ Rifampin ☐ Fluoroquinolone ☐ Linezolid ☐ Bactrim ☐ Not reported

☐Other: ……..

Dosage ATB1: ……

Detail ATB2: ☐ Rifampin ☐ Fluoroquinolone ☐ Linezolid ☐ Bactrim ☐ Not reported

☐Other: ……

☐ NA

Dosage ATB2: ……

☐ NA

Total duration of treatment:☐ 3 months for Hip, 6 months for knee (3H/6K) ☐ 3months (3M) ☐ 6weeks (6W) ☐ Not standardized ☐ Not reported ☐Other: ……

EXPERIMENTAL GROUP

Group 1:

Oral antibiotic treatment: ☐ Monotherapy ☐ Dual therapy

If Dual therapy: ☐ Rifampin and Fluoroquinolones (FQ)

☐ Rifampin combination without FQ

☐ Combination without Rifampin

☐ Other: ……

Detail ATB1: ☐ Rifampin ☐ Fluoroquinolone ☐ Linezolid ☐ Bactrim ☐ Not reported

☐Other: ……

Dosage ATB1: ……

Detail ATB2: ☐ Rifampin ☐ Fluoroquinolone ☐ Linezolid ☐ Bactrim ☐ Not reported

☐Other: ……

☐ NA

Dosage ATB2: ……

☐ NA

Total duration of treatment: ☐ 3 months for Hip, 6 months for knee (3H/6K) ☐ 3months (3M) ☐ 6weeks (6W) ☐ Not standardized ☐ Not reported ☐Other: ……

Group 2:

Oral antibiotic treatment: ☐ Monotherapy ☐ Dual therapy

If Dual therapy: ☐ Rifampin and Fluoroquinolones (FQ)

☐ Rifampin combination without FQ

☐ Combination without Rifampin

☐ Other: ……

Detail ATB1: ☐ Rifampin ☐ Fluoroquinolone ☐ Linezolid ☐ Bactrim ☐ Not reported

☐Other: ……

Dosage ATB1: ……

Detail ATB2: ☐ Rifampin ☐ Fluoroquinolone ☐ Linezolid ☐ Bactrim ☐ Not reported

☐Other: ……

☐ NA

Dosage ATB2: ……

☐ NA

Total duration of treatment: ☐ 3 months for Hip, 6 months for knee (3H/6K) ☐ 3months (3M) ☐ 6weeks (6W) ☐ Not standardized ☐ Not reported ☐Other: ……

Group 3:

Oral antibiotic treatment: ☐ Monotherapy ☐ Dual therapy

If Dual therapy: ☐ Rifampin and Fluoroquinolones (FQ)

☐ Rifampin combination without FQ

☐ Combination without Rifampin

☐ Other: ……

Detail ATB1: ☐ Rifampin ☐ Fluoroquinolone ☐ Linezolid ☐ Bactrim ☐ Not reported

☐Other: ……

Dosage ATB1: ……

Detail ATB2: ☐ Rifampin ☐ Fluoroquinolone ☐ Linezolid ☐ Bactrim ☐ Not reported

☐Other: ……

☐ NA

Dosage ATB2: ……

☐ NA

Total duration of treatment: ☐ 3 months for Hip, 6 months for knee (3H/6K) ☐ 3months (3M) ☐ 6weeks (6W) ☐ Not standardized ☐ Not reported ☐Other: ……

CHARACTERISTICS AT BASELINE

		Control	Experimental 1	Experimental 2	Experimental 3	Overall
Number of participants with PJI managed by DAIR due to Staph.		……	……	……	……	……
Age of participants (years)	☐mean ☐median	……	……	……	……	……
	☐SD ☐SE ☐range ☐IQR	……	……	……	……	……
Gender – male	☐percent ☐N	……	……	……	……	……
ASA Score	≤ 2 (N)	……	……	……	……	……
	> 2	……	……	……	……	……
CRP presurgery	☐mean ☐median	……	……	……	……	……
	☐SD ☐SE ☐range ☐IQR	……	……	……	……	……
Body Mass Index kg/m2	☐mean ☐median	……	……	……	……	……
	☐SD ☐SE ☐range ☐IQR	……	……	……	……	……
Time to switch to oral treatment	☐mean ☐median	……	……	……	……	……
	☐SD ☐SE ☐range ☐IQR	……	……	……	……	……
Diabetes mellitus (N)		……	……	……	……	……
Hip/knee/Shoulder (N/N/N)		……	……	……	……	……
Monomicrobial (N)		……	……	……	……	……
SAMS/SARM (N)		……	……	……	……	……

Results

		Control	Experimental 1	Experimental 2	Experimental 3
Included patients		……	……	……	……
Analyzed patients		……	……	……	……
Patients who **completed the trial**		……	……	……	……
Remission at 1 years (N)	Number of patients	……	……	……	……
	Adjusted ☐OR ☐RR ☐HR		……	……	……
	95% confidence interval		……	……	……
Remission at 2 years (N)	Number of patients	……	……	……	……
	Adjusted ☐OR ☐RR ☐HR		……	……	……
	95% confidence interval		……	……	……
At 1 year					
Number of patients with adverse event					
Number of patients with early cessation of treatment					
Number of patients with resistance					
Functional scale	☐mean ☐median	……	……	……	……
	☐SD ☐SE ☐range ☐IQR	……	……	……	……
Quality of life scale	☐mean ☐median	……	……	……	……
	☐SD ☐SE ☐range ☐IQR	……	……	……	……
At 2 years					
Number of patients with adverse event					
Number of patients with early cessation of treatment					
Number of patients with resistance					
Functional scale	☐mean ☐median	……	……	……	……
	☐SD ☐SE ☐range ☐IQR	……	……	……	……
Quality of life scale	☐mean ☐median	……	……	……	……
	☐SD ☐SE ☐range ☐IQR	……	……	……	……

Functional scale used – name: ……

Quality of life scale used – name: ……

If observational study – type of adjustment for main outcome:

☐regression ☐propensity score ☐No adjustment ☐NA ☐No adjustment: …….

Cofounding factor considered: ……..

Results subcategory *Staphylococcus* if both SA AND CNS

SA

		Control	Experimental 1	Experimental 2	Experimental 3
Included patients		.....	.....	.....	.....
Analyzed patients		.....	.....	.....	.....
Patients who **completed the trial**		.....	.....	.....	.....
Remission at 1 years (N)	Number of patients	.....	.....	.....	.....
	Adjusted ☐OR ☐RR ☐HR	.....	.....	.....	.....
	95% confidence interval	.....	.....	.....	.....
Remission at 2 years (N)	Number of patients	.....	.....	.....	.....
	Adjusted ☐OR ☐RR ☐HR	.....	.....	.....	.....
	95% confidence interval	.....	.....	.....	.....
At 1 year					
Number of patients with adverse event					
Number of patients with early cessation of treatment					
Number of patients with resistance					
Functional scale	☐mean ☐median	.....	.....	.....	.....
	☐SD ☐SE ☐range ☐IQR	.....	.....	.....	.....
Quality of life scale	☐mean ☐median	.....	.....	.....	.....
	☐SD ☐SE ☐range ☐IQR	.....	.....	.....	.....
At 2 years					
Number of patients with adverse event					
Number of patients with early cessation of treatment					
Number of patients with resistance					
Functional scale	☐mean ☐median	.....	.....	.....	.....
	☐SD ☐SE ☐range ☐IQR	.....	.....	.....	.....
Quality of life scale	☐mean ☐median	.....	.....	.....	.....
	☐SD ☐SE ☐range ☐IQR	.....	.....	.....	.....

Functional scale used – name: ……

Quality of life scale used – name: ……

If observational study – type of adjustment:

☐regression ☐propensity score ☐No adjustment ☐NA ☐No adjustment: ……

Cofounding factor considered: ……

CNS

		Control	Experimental 1	Experimental 2	Experimental 3
Included patients		……	……	……	……
Analyzed patients		……	……	……	……
Patients who **completed the trial**		……	……	……	……
Remission at 1 years (N)	Number of patients	……	……	……	……
	Adjusted ☐OR ☐RR ☐HR	……	……	……	……
	95% confidence interval	……	……	……	……
Remission at 2 years (N)	Number of patients	……	……	……	……
	Adjusted ☐OR ☐RR ☐HR	……	……	……	……
	95% confidence interval	……	……	……	……
At 1 year					
Number of patients with adverse event					
Number of patients with early cessation of treatment					
Number of patients with resistance					
Functional scale	☐mean ☐median	……	……	……	……
	☐SD ☐SE ☐range ☐IQR	……	……	……	……
Quality of life scale	☐mean ☐median	……	……	……	……
	☐SD ☐SE ☐range ☐IQR	……	……	……	……
At 2 years					
Number of patients with adverse event					
Number of patients with early cessation of treatment					
Number of patients with resistance					
Functional scale	☐mean ☐median	……	……	……	……
	☐SD ☐SE ☐range ☐IQR	……	……	……	……
Quality of life scale	☐mean ☐median	……	……	……	……
	☐SD ☐SE ☐range ☐IQR	……	……	……	……

Functional scale used – name: ….……

Quality of life scale used – name: ……

If observational study – type of adjustment:

☐regression ☐propensity score ☐No adjustment ☐NA ☐No adjustment: ……

Cofounding factor considered: ……

Results subcategory *location of prosthesis*

Knee

		Control	Experimental 1	Experimental 2	Experimental 3
Included patients		.....	.....	.....	.....
Analyzed patients		.....	.....	.....	.....
Patients who **completed the trial**		.....	.....	.....	.....
Remission at 1 years (N)	Number of patients	.....	.....	.....	.....
	Adjusted ☐OR ☐RR ☐HR	.....	.....	.....	.....
	95% confidence interval	.....	.....	.....	.....
Remission at 2 years (N)	Number of patients	.....	.....	.....	.....
	Adjusted ☐OR ☐RR ☐HR	.....	.....	.....	.....
	95% confidence interval	.....	.....	.....	.....
At 1 year					
Number of patients with adverse event					
Number of patients with early cessation of treatment					
Number of patients with resistance					
Functional scale	☐mean ☐median	.....	.....	.....	.....
	☐SD ☐SE ☐range ☐IQR	.....	.....	.....	.....
Quality of life scale	☐mean ☐median	.....	.....	.....	.....
	☐SD ☐SE ☐range ☐IQR	.....	.....	.....	.....
At 2 years					
Number of patients with adverse event					
Number of patients with early cessation of treatment					
Number of patients with resistance					
Functional scale	☐mean ☐median	.....	.....	.....	.....
	☐SD ☐SE ☐range ☐IQR	.....	.....	.....	.....
Quality of life scale	☐mean ☐median	.....	.....	.....	.....
	☐SD ☐SE ☐range ☐IQR	.....	.....	.....	.....

Functional scale used – name: ….……

Quality of life scale used – name: ……

If observational study – type of adjustment:

☐regression ☐propensity score ☐No adjustment ☐NA☐No adjustment: ……

Cofounding factor considered: ……

Hip

		Control	Experimental 1	Experimental 2	Experimental 3
Included patients		……	……	……	……
Analyzed patients		……	……	……	……
Patients who **completed the trial**		……	……	……	……
Remission at 1 years (N)	Number of patients	……	……	……	……
	Adjusted ☐OR ☐RR ☐HR	……	……	……	……
	95% confidence interval	……	……	……	……
Remission at 2 years (N)	Number of patients	……	……	……	……
	Adjusted ☐OR ☐RR ☐HR	……	……	……	……
	95% confidence interval	……	……	……	……
At 1 year					
Number of patients with adverse event					
Number of patients with early cessation of treatment					
Number of patients with resistance					
Functional scale	☐mean ☐median	……	……	……	……
	☐SD ☐SE ☐range ☐IQR	……	……	……	……
Quality of life scale	☐mean ☐median	……	……	……	……
	☐SD ☐SE ☐range ☐IQR	……	……	……	……
At 2 years					
Number of patients with adverse event					
Number of patients with early cessation of treatment					
Number of patients with resistance					
Functional scale	☐mean ☐median	……	……	……	……
	☐SD ☐SE ☐range ☐IQR	……	……	……	……

Quality of life scale	☐mean ☐median	……	……	……	……
	☐SD ☐SE ☐range ☐IQR	……	……	……	……

Functional scale used – name: ……

Quality of life scale used – name: ……

If observational study – type of adjustment:

☐regression ☐propensity score ☐No adjustment ☐NA ☐No adjustment:
……

Cofounding factor considered:
……

APPENDIX 3 – Antimicrobial regimens & outcomes definition

Summary:

Table 1: antimicrobial regimens and dosages used *(NR: dosage not reported; max: maximum)*

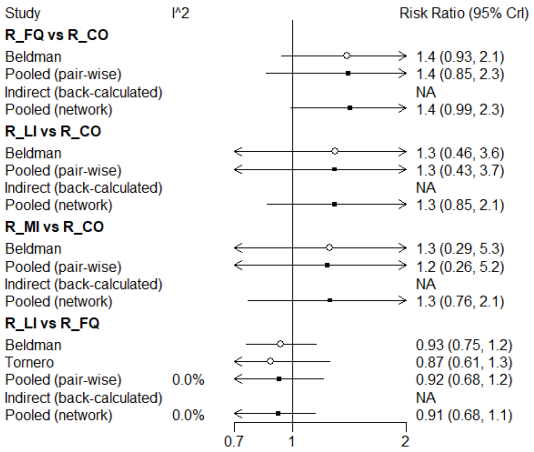
Study	Control treatment	Experimental treatment	Experimental treatment	Experimental treatment
Karlsen (2020)	Rifampin: 300mg /8h Cloxacillin: 1g /6h	Cloxacillin: 1g /6h		
Soriano (2006)	Rifampin: 600 mg/D Levofloxacin: 500 mg/D	Rifampin: 600 mg/D Clindamycin: 300 mg/8h		
Vilchez (2010)	Rifampin: 600 mg/24D Levofloxacin: 500 mg/D	Rifampin: 600 mg/D Clindamycin: 300 mg/8h	Rifampin: 600 mg/D Cotrimoxazole: 800 mg/12h	Levofloxacin: 500 mg/12h Cotrimoxazole: 800 mg/12h
		Rifampin: 600 mg/D Linezolid: 600 mg/12h	Levofloxacin: 500 mg/12h Linezolid: 600 mg/12h	
Senneville (2011)	Rifampin: 20mg/kg in divided dose given twice daily - max 1800mg/D Levofloxacin: NR	Linezolid: NR		
Tornero (2013)	Rifampin: 600 mg/D Levofloxacin: 500 mg/D	Rifampin: 600 mg/D Linezolid: NR		
Beldman (2021)	Rifampin: 600 mg/D or 450 mg/12h Levofloxacin: NR	Rifampin: 600 mg/D or 450 mg/12h Ciprofloxacin: NR	Rifampin: 600 mg/D or 450 mg/12h Moxifloxacin: NR	Rifampin: 600 mg/D or 450 mg/12h Clindamycin: NR
		Rifampin: 600 mg/D or 450 mg/12h Linezolid: NR	Rifampin: 600 mg/D or 450 mg/12h Cotrimoxazole: NR	Rifampin: 600 mg/D or 450 mg/12h Minocycline: NR

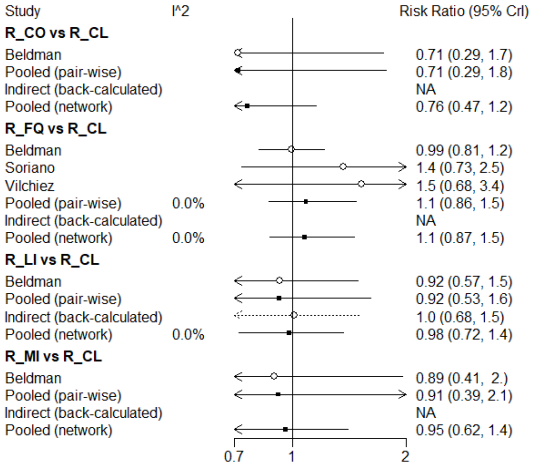
Table 2: Outcomes used and definitions *(Y: year(s). ESR: erythrocyte sedimentation rate)*

Study	Main Outcome	Remission	Failure	Follow up
Karlsen (2020)	Remission	1) Lack of clinical signs and symptoms of PJI : fever, joint pain, erythema, warmth of the skin around the incision, and sinus tract, 2) CRP < 10mg/ml, ESR as prior to index operation, 3) no radiological signs of loosening	1) Confirmed failure: Re-revision with the isolation of the initial or other microorganisms from a minimum of two intraoperative tissue specimens, 2) Probably failure: clinical signs and symptoms of local infection without microbiological documentation, repeat DAIR procedure	2Y
Soriano (2006)	Remission	1) Asymptomatic, prosthesis functioning well, CRP < 1 mg⁄ mL or, 2) Patient developed a non-septic complication that required prosthesis replacement and cultures of deep tissues negative.	1) Inflammatory signs and high CRP levels remained during treatment or, 2) Reappeared after completing treatment.	2Y
Vilchez (2010)	Remission vs Failure	Patient had no symptoms of infection, the prosthesis was retained and, CRP was ≤1 mg/dL.	1) When inflammatory signs and high CRP remained during treatment or, 2) Re-appeared after completing it (relapse or re-infection depending on the microorganism isolated) or, 3) When the patient developed an aseptic loosening that required the exchange of prosthesis, but deep samples taken during surgery were negative. Not considerd failure: need for a second debridement, within the first 10 days after the first one.	2Y
Senneville (2011)	Remission vs Failure	1) absence of local or systemic signs of infection assessed during the most recent contact with the patient and 2) Absence of the need to reoperate or, 3) Absence of the need to administer antibiotic therapy directed to the initial infected site from the end of treatment to the most recent contact.	Any other outcome, including death.	2Y
Tornero (2013)	Remission vs Failure	Patient had no symptoms of infection, the prosthesis was retained, and CRP was <1 mg/dl.	1) When inflammatory signs and high CRP remained during treatment and the patient needed a second surgery (second debridement or prosthesis removal) or, 2) When symptoms re-appeared after completing treatment. Not considered failure: when the patient developed an aseptic loosening that required the prosthesis to be exchanged and deep samples taken during surgery were found to be negative.	2Y
Beldman (2021)	Failure		1) Need for any further surgical procedure related to infection (i.e. a second surgical debridement, implant removal or amputation), PJI-related death or, 2) Need for long-term suppressive antimicrobial treatment due to persistent clinical signs of infection.	1Y

APPENDIX 4 – Pair-wise analysis, Consistency and Sensitive analysis

Summary:





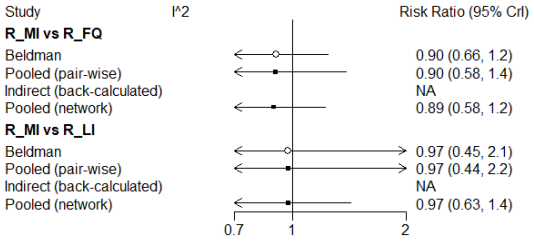


Figure 1. Pairwise and consistency

Table 1. League table of pairwise comparisons in network meta-analysis for remission (5% of failure added to R_FQ group of Beldman)

R_FQ				
1.06 (0.71, 2.00)	R_CL			
1.09 (0.54, 2.60)	1.03 (0.45, 2.20)	R_MI		
1.07 (0.64, 2.08)	1.02 (0.49, 1.90)	0.98 (0.43, 2.18)	R_LI	
1.38 (0.69, 3.34)	1.30 (0.58, 2.85)	1.25 (0.51, 3.12)	1.28 (0.57, 3.00)	R_CO

Table 2. League table of pairwise comparisons in network meta-analysis for remission, (5% of failure added to R_CL group of Beldman)

R_FQ				
1.13 (0.81, 1.92)	R_CL			
1.12 (0.65, 2.31)	0.98 (0.49, 1.90)	R_MI		
1.09 (0.71, 1.85)	0.96 (0.52, 1.61)	0.97 (0.49, 1.87)	R_LI	
1.41 (0.78, 2.93)	1.23 (0.62, 2.46)	1.25 (0.59, 2.72)	1.29 (0.66, 2.67)	R_CO

Table 3. League table of pairwise comparisons in network meta-analysis for remission (5% of failure added to R_MI group of Beldman)

R_FQ				
1.07 (0.75, 1.88)	R_CL			
1.22 (0.65, 2.58)	1.13 (0.54, 2.25)	R_MI		
1.29 (0.66, 2.67)	1.02 (0.54, 1.77)	0.91 (0.44, 1.44)	R_LI	
1.42 (0.76, 3.10)	1.38 (0.62, 2.70)	1.17 (0.52, 2.66)	1.29 (0.63, 2.76)	R_CO

Table 4. League table of pairwise comparisons in network meta-analysis for remission (5% of failure added to R_LI group of Beldman)

R_FQ				
1.08 (0.76, 1.92)	R_CL			
1.13 (0.61, 2.37)	1.05 (0.49, 2.01)	R_MI		
1.15 (0.74, 2.05)	1.07 (0.56, 1.85)	1.02 (0.450, 2.07)	R_LI	
1.41 (0.75, 3.06)	1.31 (0.62, 2.61)	1.25 (0.57, 2.82)	1.22 (0.58, 2.58)	R_CO

Table 5. League table of pairwise comparisons in network meta-analysis for remission (5% of failure added to R_CO group of Beldman)

R_FQ				
1.08 (0.78, 1.90)	R_CL			
1.13 (0.64, 2.38)	1.05 (0.52, 2.05)	R_MI		
1.10 (0.71, 1.93)	1.02 (0.54, 1.74)	0.98 (0.48, 1.93)	R_LI	
1.56 (0.83, 3.37)	1.41 (0.67, 2.87)	1.35 (0.62, 3.02)	1.39 (0.69, 2.99)	R_CO

Table 6. League table of pairwise comparisons in network meta-analysis for remission (5% of failure added to all groups of Beldman)

R_FQ				
1.11 (0.77, 1.92)	R_CL			
1.14 (0.62, 2.45)	1.05 (0.52, 2.05)	R_MI		
1.11 (0.71, 1.92)	1.00 (0.54, 1.73)	0.97 (0.45, 1.95)	R_LI	
1.43 (0.76, 3.09)	1.29 (0.62, 2.64)	1.25 (0.55, 2.84)	1.29 (0.63, 2.78)	R_CO

APPENDIX 5 – Risk of bias assessment

Summary:

Table 1. ROB2 – Karlsen 2021

Unique ID	1	**Study ID**	Karlsen		
Ref or Label	Karlsen_2020	**Aim**	assignment to intervention (the 'intention-to-treat' effect)		
Experimental	RWF	**Comparator**	Monotherapy	**Source**	Journal article(s)
Outcome	Failure	**Results**	1,3	**Weight**	1

Domain	Signalling question	Response	Comments
Bias arising from the randomization process	1.1 Was the allocation sequence random?	Y	Randomization was stratified by center and performed generator by a randomization by blocks of 10 generator. No mention of allocation concealment used
	1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?	Y	
	1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?	N	No imbalances are apparent
	Risk of bias judgement	**Low**	
Bias due to deviations from intended interventions	2.1.Were participants aware of their assigned intervention during the trial?	Y	Open-label trial
	2.2.Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	Y	
	2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the experimental context?	PN	An increasing trend towards using rifampin developed in the orthopedic society during the study period but carer did not switch monotherapy to rifampin group
	2.4 If Y/PY to 2.3: Were these deviations likely to have affected the outcome?	NA	
	2.5. If Y/PY/NI to 2.4: Were these deviations from intended intervention balanced between groups?	NA	7 patients stopped rifampin in rifamin group, 6 patients stopped their initial regimen in monotherapy group
	2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?	N	Authors excluded trial patients who did not receive their assignment intervention
	2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized?	PY	11/65 (17%) where excluded due to deviation from the intended intervention
	Risk of bias judgement	**Some concerns**	
Bias due to missing outcome data	3.1 Were data for this outcome available for all, or nearly all, participants randomized?	N	17/65 (26%) dropped out before completion of treatment. Although reasons for the dropout explained, only per protocol analysis was performed
	3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data?	PY	proportion of participants with missing data is similar between the intervention groups
	3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	NA	
	3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?	NA	
	Risk of bias judgement	**Low**	
Bias in measurement of the outcome	4.1 Was the method of measuring the outcome inappropriate?	N	Definition of failure include: probably failure defined as clinical signs and symptoms of local infection but without microbiological documentation. It is not a usual definition of failure and as it is a subjective outcome and this is an open label, there is a high risk of bias of measurement.
	4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	PY	Outcome is subjective and this is an open label, there is a high risk of bias of measurement.
	4.3 Were outcome assessors aware of the intervention received by study participants?	NA	

	4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	NA	
	4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	NA	
	Risk of bias judgement	**High**	
Bias in selection of the reported result	5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?	Y	Authors planned and performed a modify intention-to-treat analysis, but it was a per protocol
	5.2 ... multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	N	No
	5.3 ... multiple eligible analyses of the data?	N	No
	Risk of bias judgement	**Some concerns**	
Overall bias	**Risk of bias judgement**	**High**	

Table 2. ROBINS – Soriano 2006

	Evaluation (Low / Moderate / Serious / Critical / NI)	Support for rating (text)
Bias due to Confounding	**Critical**	The authors did not report confounders by treatment received and did not adjust for our outcomes
Bias in selection of participants into the study	**Low**	All participants who would have been eligible for the target trial were included in the study; and for each participant, start of follow up and start of intervention coincided.
Bias in classification of intervention	**Low**	Intervention status is well defined;(ii) and intervention definition is based solely on information collected at the time of intervention.
Bias due to deviations from intended interventions	**Low**	Any deviations from intended intervention reflected usual practice
Bias due to missing data	**Low**	Data were complete.
Bias in measurement of outcomes	**Serious**	The outcome measure was subjective (i.e. vulnerable to influence by knowledge of the intervention received by study participants); and the outcome was assessed by assessors aware of the intervention received by study participants;
Bias in selection of the reported result	**Moderate**	The outcome measurements and analyses are clearly defined and both internally and externally consistent but there was no pre-registered protocol; and there is no indication of selection of the reported analysis from among multiple analyses; and there is no indication of selection of the cohort or subgroups for analysis and reporting on the basis of the results.
Overall bias	**Critical**	The study is judged to be at critical risk of bias in at least one domain.

Table 3. ROBINS – Vilchez 2010

	Evaluation (Low / Moderate / Serious / Critical / NI)	Support for rating (text)
Bias due to Confounding	**Critical**	The authors did not report confounders by treatment received and did not adjust for our outcomes
Bias in selection of participants into the study	**Low**	All participants who would have been eligible for the target trial were included in the study; and for each participant, start of follow up and start of intervention coincided.
Bias in classification of intervention	**Low**	Intervention status is well defined; (ii) and intervention definition is based solely on information collected at the time of intervention.
Bias due to deviations from intended interventions	**Low**	Any deviations from intended intervention reflected usual practice
Bias due to missing data	**Low**	Data were complete.
Bias in measurement of outcomes	**Serious**	The outcome measure was subjective (i.e. vulnerable to influence by knowledge of the intervention received by study participants); and the outcome was assessed by assessors aware of the intervention received by study participants;
Bias in selection of the reported result	**Moderate**	The outcome measurements and analyses are clearly defined and both internally and externally consistent but there was no pre-registered protocol; and there is no indication of selection of the reported analysis from among multiple analyses; and there is no indication of selection of the cohort or subgroups for analysis and reporting on the basis of the results.
Overall bias	**Critical**	The study is judged to be at critical risk of bias in at least one domain.

Table 4. ROBINS – Senneville 2010

	Evaluation (Low / Moderate / Serious / Critical / NI)	Support for rating (text)
Bias due to Confounding	**Critical**	The authors did not report confounders by treatment received and did not adjust for our outcomes
Bias in selection of participants into the study	**Low**	All participants who would have been eligible for the target trial were included in the study; and for each participant, start of follow up and start of intervention coincided.
Bias in classification of intervention	**Low**	Intervention status is well defined;(ii) and intervention definition is based solely on information collected at the time of intervention.
Bias due to deviations from intended interventions	**Low**	Any deviations from intended intervention reflected usual practice
Bias due to missing data	**Low**	Data were complete.
Bias in measurement of outcomes	**Serious**	The outcome measure was subjective (i.e. vulnerable to influence by knowledge of the intervention received by study participants); and the outcome was assessed by assessors aware of the intervention received by study participants;
Bias in selection of the reported result	**Moderate**	The outcome measurements and analyses are clearly defined and both internally and externally consistent but there was no pre-registered protocol; and there is no indication of selection of the reported analysis from among multiple analyses; and there is no indication of selection of the cohort or subgroups for analysis and reporting on the basis of the results.
Overall bias	**Critical**	The study is judged to be at critical risk of bias in at least one domain.

Table 5. ROBINS – Tornero 2013

	Evaluation (Low / Moderate / Serious / Critical / NI)	Support for rating (text)
Bias due to Confounding	**Critical**	The authors did not report confounders by treatment received and did not adjust for our outcomes
Bias in selection of participants into the study	**Low**	All participants who would have been eligible for the target trial were included in the study; and for each participant, start of follow up and start of intervention coincided.
Bias in classification of intervention	**Low**	Intervention status is well defined; (ii) and intervention definition is based solely on information collected at the time of intervention.
Bias due to deviations from intended interventions	**Low**	Any deviations from intended intervention reflected usual practice
Bias due to missing data	**Low**	Data were complete.
Bias in measurement of outcomes	**Serious**	The outcome measure was subjective (i.e. vulnerable to influence by knowledge of the intervention received by study participants); and the outcome was assessed by assessors aware of the intervention received by study participants;
Bias in selection of the reported result	**Moderate**	The outcome measurements and analyses are clearly defined and both internally and externally consistent but there was no pre-registered protocol; and there is no indication of selection of the reported analysis from among multiple analyses; and there is no indication of selection of the cohort or subgroups for analysis and reporting on the basis of the results.
Overall bias	**Critical**	The study is judged to be at critical risk of bias in at least one domain.

Table 6. ROBINS – Beldman 2021

	Evaluation (Low / Moderate / Serious / Critical / NI)	Support for rating (text)
Bias due to Confounding	**Critical**	The authors did not report confounders by treatment received and did not adjust for our outcomes
Bias in selection of participants into the study	**Critical**	Selection into the study was very strongly related to intervention four centers using rifampin were compared with only one center not using rifampin and they excluded patients in 'rifampin-centers' who were not treated with rifampin.
Bias in classification of intervention	**Low**	Intervention status is well defined;(ii) and intervention definition is based solely on information collected at the time of intervention.
Bias due to deviations from intended interventions	**Low**	Any deviations from intended intervention reflected usual practice
Bias due to missing data	**Low**	Data were complete.
Bias in measurement of outcomes	**Serious**	The outcome measure was subjective (i.e. vulnerable to influence by knowledge of the intervention received by study participants); and the outcome was assessed by assessors aware of the intervention received by study participants;
Bias in selection of the reported result	**Moderate**	The outcome measurements and analyses are clearly defined and both internally and externally consistent but there was no pre-registered protocol; and there is no indication of selection of the reported analysis from among multiple analyses; and there is no indication of selection of the cohort or subgroups for analysis and reporting on the basis of the results.
Overall bias	**Critical**	The study is judged to be at critical risk of bias in at least one domain.

AUTEUR : Nom : GACHET **Prénom : Benoit**

Date de soutenance : 29/06/2022

Titre de la thèse : Traitements antibiotiques oraux des infections de prothèses ostéoarticulaires à staphylocoque prises en charge par arthrotomie, synovectomie, lavage : revue systématique et méta-analyse en réseau

Thèse - Médecine - Lille « 2022 »

Cadre de classement : *Maladies infectieuses et tropicales*

DES + spécialité : *Médecine interne + Maladies infectieuses et tropicales*

Mots-clés : méta-analyse en réseau, prothèse ostéoarticulaire, infection, antibiotique

Résumé :
Introduction : Le traitement antibiotique oral des infections de prothèses ostéoarticulaires à staphylocoque recommandé en première intention associe la rifampicine et une fluoroquinolone. Lorsque les fluoroquinolones ou la rifampicine ne peuvent être utilisées, plusieurs molécules avec une bonne diffusion osseuse sont disponibles mais il n'existe pas de hiérarchisation de ces schémas thérapeutiques.
Méthode : Nous avons réalisé une revue systématique et une méta-analyse en réseau des traitements antibiotiques oraux des infections de prothèses ostéoarticulaires à staphylocoque prises en charge par arthrotomie, synovectomie, lavage et conservation de l'implant.
Résultats : 1 essai clinique randomisé et 5 essais cliniques non randomisés ont évalué au total 10 schémas thérapeutiques. 6 schémas thérapeutiques utilisaient une combinaison Rifampicine avec un compagnon (Fluoroquinolone, Clindamycine, Cotrimoxazole, Linézolide, Minocycline, Cloxacilline), 2 une combinaison d'antibiotiques sans rifampicine (Levofloxacine-Linézolide ou Levofloxacine-Cotrimoxazole) et 2 schémas une monothérapie (Linézolide ou Cloxacilline). Nous avons réalisé une méta-analyse en incluant uniquement les essais cliniques non randomisés et nous n'avons pu comparer que 5 schémas thérapeutiques, l'effectif étant trop faible pour les autres schémas thérapeutiques et ne permettait pas au modèle de converger. Aucun des schémas thérapeutiques n'était significativement supérieur à un autre en termes de rémission. Cependant, l'association Rifamicine-Fluorquoquinolone était supérieure aux 4 autres et l'association Rifampicine-Cotrimoxazole était moins efficace que les 4 autres. Les associations Rifampicine-Linézolide, Rifampicine-Clindamycine, Rifampicine-Minocycline avaient sensiblement le même taux de rémission.
Conclusion : L'association Rifampicine-Fluoroquinolone est celle qui a été la plus étudiée et qui semble être la plus efficace. Lorsque les fluoroquinolones ne peuvent être utilisées, les associations Rifamicine-Linézolide, Rifamicine-Minocycline ou Rifamicine-Clindamycine semblent les plus efficaces. Néanmoins, les données actuelles reposent essentiellement sur des essais non randomisés et nous n'avons pas mis en évidence de différence statistiquement significative entre les traitements. De nouvelles études sont nécessaires pour établir une meilleure hiérarchisation et explorer d'autres schémas thérapeutiques.

<u>Composition du Jury</u> :

Président : Éric SENNEVILLE
Assesseurs : Fanny VUOTTO, Henri MIGAUD
Directeur de thèse : Olivier ROBINEAU