

## The Dutch Working Party on Antibiotic Policy (SWAB) Guideline for the Antimicrobial Treatment of Periprosthetic Joint Infections

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## **Part I: General principles**

## Introduction

An infection of a prosthetic joint (PJI) is a serious complication, carrying high morbidity and mortality for the patient and substantial health care costs. Of the 70,000 patients in the Netherlands who undergo hip or knee arthroplasty each year, about 1.5-2.0% develop a PJI.[1] Infection is the main reason for hip revision within one year after arthroplasty.[1] The incidence of PJI is expected to increase in the years to come with the ageing of society, an increasing number of primary implantations being performed and the number of cumulative arthroplasties that remain in place.[2]

The surgical management of PJI is dependent on the duration of symptoms and the time since the implantation of the prosthesis. Surgical treatment is combined with tailored antibiotic treatment based on susceptibility test results of the cultured micro-organisms. In some cases of PJI, in which surgical debridement is not possible, or is inadequately performed, long-term suppressive antibiotic treatment is prescribed to patients. In recent years a vast quantity of studies have evaluated the antimicrobial management of complex PJI. However, guidelines on the antimicrobial treatment of PJI remain scarce [3-5] and are highly dependent on local preferences and practices. In this SWAB guideline we aim to provide guidance to clinicians in the Netherlands on the antimicrobial management of patients with PJI and systematically review the evidence for some of the most pressing clinical questions related to this topic.

The Dutch Working Party on Antibiotic Policy (SWAB), established by the Dutch Society for Infectious Diseases, the Dutch Society for Medical Microbiology and the Dutch Association of Hospital Pharmacists, coordinates activities in the Netherlands aimed at optimization of antibiotic use, containment of the development of antimicrobial resistance, and limitation of the costs of antibiotic use. By means of the evidence-based development of guidelines, SWAB offers local antibiotic and formulary committees a guideline for the development of their own local antibiotic policy. SWAB yearly reports on the use of antibiotics, on trends in antimicrobial resistance and on antimicrobial stewardship activities in The Netherlands in NethMap (available from www.swab.nl), in collaboration with the National Institute for Public Health and the Environment (RIVM-CIb).

## Scope of the guideline

This guideline will focus on antimicrobial therapy for PJI in adults for different surgical techniques and pathogens. Diagnosis of PJI, prophylactic use of antibiotics, topical antimicrobial treatment (e.g., antimicrobial-loaded cement or aminoglycoside collagen fleeces) and indications for surgical treatment lie beyond the scope of this guideline. Nevertheless, the following paragraphs contain some guidance on surgical principles for PJI. For details on surgical strategy and surgical techniques, we refer to the guidelines of the Dutch Orthopaedic Society,[6] the practice guidelines of the Infectious Diseases Society of America, [3] and the international consensus documents.[5, 7, 8]

## **Methods**

The guideline was written according to the Appraisal of Guidelines for Research & Evaluation (AGREE) instrument.[9] In addition to the AGREE instrument, the Guideline committee followed a guideline development process comparable to that of the Infectious Diseases Society of America (IDSA), which includes a systematic method of grading both the quality of evidence (very low, low, moderate, and

high) and the strength of the recommendation (conditional or strong).[10] The quality of evidence per outcome variable was graded according to the GRADE (Grading of Recommendations Assessment, Development and Evaluation) system, adopted by SWAB.[11] In line with the GRADE format, several clinical questions were formulated and structured in the patient-intervention-comparison-outcome (PICO) format. Altogether, the guideline committee formulated 16 clinical questions (Appendix A) of importance for antimicrobial treatment in current Dutch practices. The guideline committee decided to do a systematic literature search for these 16 clinical questions. The guideline committee also decided to give some general recommendations for empirical treatment of PJI. These general recommendations were not based on a systematic literature search but based on the expertise available in the committee and on the known epidemiology of causative microorganisms in The Netherlands. The answers to the other questions were plenary discussed in the guideline committee taking into account recommendations of existing guidelines.[3-6, 8]

Wide search terms were used for the literature review (see Appendix A). Databases from Pubmed, Embase, Cochrane and trial registers were reviewed. Next, articles were screened based on title and abstract for full text review without any time or language restriction. Studies with comparison groups (Randomised controlled trials, cohort studies and case-control studies) and systematic reviews were included. Two independent members of the guideline committee carried out the abstract selection. The full text review and the evidence tables were carried out by independent couples of the guideline committee members. Discrepancies between two committee members were resolved through discussion. The committee recognised that comparison of studies that evaluated outcome of PJI after surgical and antimicrobial treatment for prosthetic joint infection was hampered by the fact that different definitions for cure and failure are used in the available literature. We chose to use the definitions as used in the articles that were included, thereby acknowledging that differences in cure rate must be weighed against the definitions that were used. After articles were selected, the quality of evidence was rated. Quality of evidence is determined by several factors, the most important of these being study design.[11] The remaining factors (e.g., risk of bias) can downgrade or upgrade the quality of evidence based on design. For example, an observational study with a serious risk of bias is considered to have a very low quality of evidence. Next, a recommendation was formed that was adopted after consensus by the full guideline committee was reached. The committee determined the direction, strength, and wording of the recommendation(s) for the specific clinical question. Recommendations were rated as 'for' or 'against' the particular intervention or 'either the intervention or the comparison', and the strength of each recommendation was rated as 'strong' or 'conditional'. A recommendation was defined as conditional when the committee concluded that the desirable effects of adherence to a recommendation probably outweigh the undesirable effects, but is not confident. The quality of evidence, rated as 'high' (GRADE A), 'moderate' (GRADE B), 'low' (GRADE C) or 'very low' (GRADE D) based on the critical outcome(s) reviewed for the question in accordance with GRADE, as explained above, was added to the strength of the recommendation.[11, 12] For this reason, despite the overall low quality of evidence, experience in the field and confidence in the desirable result for the patient might have led to a strong recommendation.

Some recommendations from this guideline were not based on formal literature search. These recommendations were formulated after consensus in the guideline committee and do not have a strength of recommendation or an evidence appraisal. These recommendations are labelled 'good practice statement'.

Preparation of the guideline text was carried out by a multidisciplinary committee consisting of experts delegated from their professional societies and from both academic and non-academic hospitals. The guideline committee was responsible for the preparation of this guideline. After consultation with the members of these professional societies in the Netherlands, the committee has drawn up the definitive guideline for practical use. The definitive guideline was approved by the board of SWAB June 28<sup>th</sup>, 2024. No patient input was sought for the development of this guideline.

## **Definitions and abbreviations**

In Table 1, definitions and abbreviations used in this guideline are given.

**Table 1: Definitions and abbreviations** 

Term	Abbreviation	Definition
Early acute (postoperative) periprosthetic joint infection	Early acute PJI	A periprosthetic joint infection occurring within three months after the index arthroplasty
Late acute (hematogenous) periprosthetic joint infection	Late acute PJI	A periprosthetic joint infection occurring more than three months after the index arthroplasty. Presenting with a sudden, acute onset of symptoms in a prior asymptomatic joint.
Appraisal of Guidelines for Research and Evaluation	AGREE	Instrument to provide a framework to assess the quality of guidelines, to provide a methodological strategy for the development of guidelines, and to inform what information and how information ought to be reported in guidelines.[9]
Antibiotic resistant bacteria	ARB	Bacteria resistant to various antibiotics (BRMO; bijzonder resistente micro-organismen in Dutch)
Late chronic periprosthetic joint infection	Chronic PJI	A periprosthetic joint infection occurring more than 3 months after the index arthroplasty.  Presenting with chronic pain with or without loosening of the prosthesis.
Coagulase negative staphylococci	CNS	
Culture negative PJI	CN	The patient does fulfil the EBJIS criteria for a PJI but peroperative cultures are negative.
Debridement, antibiotics and implant retention	DAIR	Treatment strategy for periprosthetic joint infection in which debridement, antibiotics and implant retention are combined [6]
Grading of Recommendations Assessment, Development, and Evaluation	GRADE	Systematic method to grade quality of evidence and strength of recommendations. see Gyatt et al.[11]
Minimal inhibitory concentration	MIC	The lowest concentration of a drug that prevents visible growth of the bacteria
Methicillin-resistant Staphylococcus aureus	MRSA	Staphylococcus aureus resistant to methicillin and other beta lactam antibiotics (with the exception of fifth generation cephalosporins e.g., ceftaroline)
Methicillin-susceptible Staphylococcus aureus	MSSA	Staphylococcus aureus sensitive to methicillin and other beta lactam antibiotics

One-stage revision	1SR	Surgical treatment for periprosthetic joint infection in which explantation of the complete prosthesis and reimplantation of a new prosthesis are conducted in one procedure
Patient-intervention- comparison-outcome	PICO	Systematic method whereby the components "patient", "intervention", "comparison", and "outcome" are used to answer a clinical question.
Periprosthetic joint infection	PJI	Clinical evidence with or without microbiological support for an infection involving a joint prosthesis and adjacent tissue.
Suppressive antibiotic therapy	SAT	The chronic use of antimicrobial therapy for a chronic PJI aimed at preventing relapse of the infection
Two-stage revision	2SR	Surgical treatment for periprosthetic joint infection in which revision of the prosthesis, defined as explantation of the complete prostheses followed by reimplantation of a new prosthesis is conducted in two procedures.

## **Implementation**

After final approval, the SWAB guidelines are published at www.swab.nl, and an executive summary is published in a peer-reviewed journal. The new guidelines form the basis of the treatment recommendations in the online national antimicrobial guide (SWAB-ID) for the prophylaxis and treatment of infectious diseases in hospitals. SWAB-ID is updated at least twice yearly, incorporating all SWAB guideline recommendations. Every hospital in the Netherlands has been offered the opportunity to obtain a custom, localised version of SWAB-ID as a local or regional online antimicrobial guide. Updates of the national version of SWAB-ID, including new guidelines, are distributed to the localised SWAB-ID guides. The implementation of national and local SWAB-ID antimicrobial guidelines and adherence to the recommendations are secured by the national Antimicrobial Stewardship Program that has been established by SWAB, the Health Inspectorate (IGJ) and the Ministry of Health (VWS) since 2013. In each hospital, an Antimicrobial Stewardship Team (Ateam) is charged with implementation and monitoring of guidelines on a daily basis.

## Funding and conflicts of interest

For the development of this guideline, the SWAB was funded by the National Institute for Public Health and the Environment (RIVM-CIb), the Netherlands.

The SWAB employs strict guidelines with regard to potential conflicts of interests, as described in the SWAB Format for Guideline Development (www.swab.nl). All members of the guideline committee complied with the SWAB policy on conflicts of interest, which requires disclosure of any financial or other interest that might be construed as constituting an actual, potential, or apparent conflict. Members of the guideline committee were provided the SWAB conflict of interest disclosure statement and were asked to identify ties to companies developing products or other parties that might be affected by the guideline. Information was requested regarding employment, honoraria, consultancies, stock ownership, research funding, and membership on company advisory

committees. The panel made decisions on a case-by-case basis as to whether an individual's role should be limited as a result of a conflict.

Potential conflicts of committee members are listed in Table 2

Table 2: Disclosure of potential conflicts of interest of committee members

Member	Potential conflicts of interest	
E.J.G. Peters	Roche Diagnostics, research funding	
S.A.V. van Asten	None to declare	
M. Wouthuyzen-Bakker	None relevant to the content of this guideline	
H. Scheper	ZonMW funding for investigator-initiated trial for antibiotic treatment of staphylococcal PJI (RiCOTTA trial)	
E. van Elzakker	None to declare	
L. Reubsaet	None to declare	
Dr. M.W. Nijhof	None to declare	
H.C. Vogely	None to declare	
G. Van der Bij	None to declare	
P. C. Jutte	None to declare	
P.D. van der Linden	None to declare	
A. Plender	None to declare	

## Applicability and validity

The guideline articulates the prevailing professional standard in 2023 and contains general recommendations for the antibiotic treatment of hospitalised adults. It is likely that most of these recommendations are also applicable to children, but this has not been formally evaluated. It is possible that these recommendations are not applicable in an individual patient case. The applicability of the guideline in clinical practice is the responsibility of the treating physician. There may be facts or circumstances which, in the interest of proper patient care, non-adherence to the guideline is desirable.

SWAB intends to revise their guidelines every 5 years. The potential need for earlier revisions will be determined by the SWAB board at annual intervals, on the basis of an examination of current literature. If necessary, the guidelines committee will be reconvened to discuss potential changes. When appropriate, the committee will recommend expedited revision of the guideline to the SWAB board. Therefore, in 2029 or earlier if necessary, the guideline will be re-evaluated.

## **Part II: Synopsis of recommendations**

# A. General recommendations not based on PICOs and systematic review of literature

The recommendations formulated in this paragraph are labelled as 'good practice statement' and are based on consensus in the guideline committee. Therefore, they do not have a strength of recommendation or an evidence appraisal.

## General principles of antimicrobial treatment of PJI

## **Recommendation:**

We recommend administering antibiotic therapy for PJI initially by the parenteral route. We recommend continuous infusion, in particular for betalactam antibiotics. An early switch to oral therapy after one week of IV treatment is recommended if the patient is clinically improving, has decreasing inflammatory parameters, has no contraindications to oral therapy and there is an appropriate oral agent available with adequate bio-availability.

Good practice statement

## Allergies to first choice antibiotics and toxicity

## **Recommendation:**

We recommend to consult the SWAB guideline 'Approach to suspected antibiotic allergy' in case of a suspected antimicrobial allergy for detailed information regarding the approach to (suspected) antibiotic allergies, and potential cross-reactivity of antibiotics.[13] Good practice statement

## **Empirical therapy**

(defined as the initial antibiotic regimen selected in the absence of definitive microbiological pathogen identification and susceptibility testing)

## **Recommendation:**

We suggest to select an empirical therapy for treating a PJI based on the suspected causative pathogens and the surgical treatment that is performed. The prescriber should take into consideration previous culture results, previous treatments and the type of surgery (which is often based on the chronicity of the infection (i.e. early acute postoperative, late acute (hematogenous) or late chronic infection (Table 3).

Good practice statement

### **Recommendation:**

In case of a DAIR for an early acute post-operative infection, we suggest to empirically treat with vancomycin and ceftriaxone to cover *Staphylococcus aureus*, streptococci, coagulase negative staphylococci (CNS), enterococci and Enterobacterales. We do not recommend to empirically cover *Pseudomonas* unless local epidemiology indicates a high prevalence.

Good practice statement

#### **Recommendation:**

In case of a DAIR for a late acute (haematogenous) infection, we suggest to treat empirically with flucloxacillin to cover *Staphylococcus aureus* and streptococci. We suggest to add ceftriaxone if the patient has a concurrent clinical presentation that is associated with Enterobacterales, like cholangitis or urosepsis (Table 3).

Good practice statement

#### **Recommendation:**

In case of a one-stage revision (1SR) for a late chronic infection we advise to give targeted treatment based on cultures. This is because a 1SR is generally only performed in patients with known causative pathogens. However, if cultures are not yet known, we suggest to treat empirically with vancomycin to cover coagulase negative staphylococci, enterococci and *Cutibacterium acnes* (Table 3). Good practice statement

## **Recommendation:**

In case of a two-stage revision (2SR) we advise to give targeted treatment after explantation of the prosthesis, based on cultures. This is because a 2SR is mostly performed in patients with already known causative pathogens and there is no prosthesis left or implanted for which immediate postoperative coverage with broad-spectrum antibiotics is warranted (Table 3). Good practice statement

## B. Specific recommendations based on PICOs and systematic review of literature

## **Culture-directed antimicrobial therapy**

## Staphylococci

PICO 1a: In a person with a PJI caused by staphylococci, is a rifampicin-based regimen more effective in achieving clinical cure?

## **Recommendation:**

We suggest to add rifampicin in the treatment of (rifampicin-susceptible) staphylococcal PJI treated with DAIR of 1SR.

Strength of recommendation: conditional, quality of evidence: low

PICO 1b: In a person with a PJI caused by staphylococci, is a non-fluoroquinolone combined with rifampicin as effective as a fluoroquinolone combined with rifampicin in achieving clinical cure?

## **Recommendation:**

We suggest, if rifampicin is used for staphylococcal infection, to combine it with a fluoroquinolone (in the absence of resistance to fluoroquinolones or rifampicin) in PJI.

Strength of recommendation: conditional, quality of evidence: low

PICO 1c: In a person with a PJI caused by methicillin resistant coagulase negative staphylococci, is initial treatment with daptomycin as effective as vancomycin in achieving clinical cure?

## **Recommendation:**

We suggest to use vancomycin, not daptomycin, as first choice of treatment for PJI caused by methicillin resistant staphylococci.

Strength of recommendation: conditional, quality of evidence: very low

## Streptococci

PICO 2a: In a person with a PJI caused by streptococci, is a rifampicin-based regimen more effective in achieving clinical cure than treatment regimens without rifampicin?

#### **Recommendation:**

We suggest not to use rifampicin for streptococcal PJI.

Strength of recommendation: conditional, quality of evidence: low

PICO 2b: In a person with a PJI caused by streptococci, is oral treatment with amoxicillin as effective as clindamycin in achieving clinical cure?

## **Recommendation:**

We suggest to use amoxicillin for streptococcal PJI.

Strength of recommendation: conditional, quality of evidence: very low

## **Enterococci**

PICO 3: In a person with a PJI caused by enterococci, is initial treatment with monotherapy as effective as a combination therapy in achieving clinical cure?

## **Recommendation:**

We suggest to treat patients with enterococcal PJI sensitive to amoxicillin either with combination therapy with amoxicillin and ceftriaxone, or with amoxicillin monotherapy.

Strength of recommendation: conditional, quality of evidence: low

## **Recommendation:**

We suggest to treat patients with amoxicillin-resistant enterococcal PJI with vancomycin monotherapy

Strength of recommendation: conditional, quality of evidence: low

## **Gram-negative bacilli**

PICO 4: In a person with a PJI caused by gram-negative bacilli, is oral treatment with trimethoprim/sulfamethoxazole as effective as oral treatment with a fluoroquinolone in achieving clinical cure?

## **Recommendation:**

We recommend to use a fluoroquinolone over trimethoprim-sulfamethoxazole in treatment of PJI caused by gram negative bacilli.

Strength of recommendation: conditional, quality of evidence: very low

## Cutibacterium (Propionibacterium) acnes

PICO 5a: In a person with a PJI caused by *Cutibacterium (Propionibacterium) acnes*, is oral treatment with amoxicillin as effective as oral treatment with clindamycin in achieving clinical cure?

### **Recommendation:**

We suggest to treat Cutibacterium acnes PJI with amoxicillin.

Strength of recommendation: conditional, quality of evidence: very low

PICO 5b: In a person with a PJI caused by *Cutibacterium (Propionibacterium) acnes*, is a rifampicin-based regimen more effective in achieving clinical cure than treatment regimens without rifampicin?

## **Recommendation:**

We suggest not to treat *Cutibacterium acnes* PJI with a rifampicin-based regimen. Strength of recommendation: conditional, quality of evidence: low

## Candida

PICO 6: In a person with a PJI caused by *Candida*, is initial treatment with fluconazole as effective as treatment with other antimycotic drugs?

## **Recommendation:**

We suggest to treat persons with a PJI caused by *Candida* species with fluconazole as initial regimen if the *Candida* is susceptible to fluconazole, the implant is exchanged, and the patient does not have candidemia. If susceptibility to azole compounds is unknown we suggest to start treatment with anidulafungin.

Strength of recommendation: conditional, quality of evidence: low

## **Culture-negative**

PICO 7: In a person with a culture-negative PJI, is a fluoroquinolone combined with rifampicin regimen as effective as any other treatment in achieving clinical cure?

## **Recommendation:**

We suggest not to use a fluoroquinolone combined with rifampicin as a standard treatment for culture-negative PJI.

Strength of recommendation: conditional, quality of evidence: very low

#### **Recommendation:**

We recommend to determine antimicrobial strategies for culture-negative PJI on an individual basis (e.g., taking into account prior antibiotic use, results of molecular testing, host characteristics and symptoms)

Strength of recommendation: strong, quality of evidence: very low

## Chronic suppressive antibiotic therapy

PICO 8: Can suppressive antibiotic therapy in a person with a PJI be stopped after 2 years?

#### **Recommendation:**

We suggest to base the decision on the duration of chronic suppressive antimicrobial therapy on an individual basis (e.g., taking into account toxicity of antibiotics and host characteristics)

Strength of recommendation: conditional, quality of evidence: very low

## **Recommendation:**

We suggest to withhold chronic antimicrobial suppressive therapy in patients with a draining sinus tract.

Strength of recommendation: conditional, quality of evidence: very low

## **Duration of therapy**

PICO 9a: In a person with an acute PJI treated with DAIR, is 6 (or 8) weeks of antibiotic therapy enough to achieve clinical cure compared with 12 weeks of antibiotic therapy?

## **Recommendation:**

We recommend to treat patients with acute PJI who undergo DAIR for 12 weeks with antibiotics Strength of recommendation: strong, quality of evidence: high

PICO 9b: In a person with a chronic PJI treated with 1SR, is 4 (or 6) weeks of antibiotic therapy enough to achieve clinical cure compared with 12 weeks of antibiotic therapy?

## **Recommendation:**

We suggest to treat patients with chronic PJI who undergo 1SR for 6 weeks, but the duration can be lengthened to 12 weeks depending on clinical circumstances.

Strength of recommendation: conditional, quality of evidence: low

## Timing of therapy

PICO 10: In a person with a chronic PJI treated with two-stage revision surgery, is antibiotic holiday/withholding of antibiotics before reimplantation more effective in achieving clinical cure compared with no antibiotic holiday?

## Recommendation:

We suggest not to delay reimplantation after finishing antibiotic treatment in 2SR. Strength of recommendation: conditional, quality of evidence: very low.

## PICO 11: In a person with an acute PJI caused by staphylococci and treated with DAIR, should you defer the start of rifampicin until the wound is no longer draining?

## **Recommendation:**

We suggest not to defer the start of rifampicin until the wound stops draining in a person with an acute PJI caused by staphylococci and treated with DAIR Strength of recommendation: strong, quality of evidence: very low.

## Recommended empirical antimicrobial treatment

Table 3. Empirical antimicrobial treatment for PJI, to be started after surgical debridement

Surgical strategy	Empirical treatment <sup>a</sup>
DAIR for early acute PJI	vancomycin 35 mg/kg continuously /24 hrb (20 mg/kg loading dose) i.v. + ceftriaxone 2 g BID i.v.
	or
	vancomycin 35 mg/kg continuously /24 hr b(20 mg/kg loading dose) i.v. +
	ceftazidime 6 g/ 24 i.v. (2 g loading dose (if need for <i>Pseudomonas</i> coverage
	according to local epidemiology)
DAIR for late acute	flucloxacillin 6 g/24 i.v. (loading dose 1g) <sup>c</sup>
hematogenous PJI	
	or
	flucloxacillin 6 g/24 i.v. (loading dose 1g) <sup>c</sup> + ceftriaxone 2 gram OD (in case of a
	clinical suspicion of an underlying abdominal focus, e.g., cholangitis, urosepsis)
1SR	Targeted therapy. If empirical therapy needed: vancomycin 35 mg/kg
	continuously /24 hrb (20 mg/kg loading dose)
2SR after explantation /	Targeted therapy
girdlestone <sup>d</sup>	

Abbreviations: 1SR, one-staged revision; 2SR, two-staged revision; DAIR, debridement, antibiotics and implant retention; g, gram; TID, three times daily

- If a patient has a concomitant bacteremia, endocarditis or candidemia, empirical treatment may need to be adjusted according to the relevant SWAB guidelines.
- For dosing regimen for obese patients and patients with impaired renal function, see SWAB-ID:
   Medicatie | SwabID (antibiotica.app)
- Antibiotic strategy may need to be changed in case of MRSA/MDRO colonisation
- It can be considered to empirically add rifampicin immediately after DAIR or 1SR for optimal bactericidal treatment of staphylococci, see also PICO 11.

<sup>&</sup>lt;sup>a</sup> General remarks when starting empirical treatment for PJI:

<sup>&</sup>lt;sup>b</sup> Alternative dosing regimen is 17.5 mg/kg BID (30 mg/kg loading dose). For therapeutic drug monitoring (TDM) of vancomycin we refer to SWAB-ID: TDM - vancomycine | SwabID (antibiotica.app).

<sup>&</sup>lt;sup>c</sup> Flucloxacillin range 6-12 g/24 hours (in case of 12 g/24 hr, loading dose 2 g).

<sup>&</sup>lt;sup>d</sup> If reimplantation of the new prosthesis takes place during the period of antibiotic treatment (a short interval) then the possibility of additional antibiotic strategy (i.e. rifampicin) after reimplantation needs to be discussed during a MDT meeting.

## Recommended targeted antimicrobial treatment for microorganisms causing PJI

## **General recommendations for targeted treatment:**

An early switch to oral therapy (after one week of IV treatment) is recommended if the patient is clinically improving, has decreasing inflammatory parameters, has no contraindications to oral therapy and if there is an appropriate oral agent available with adequate bio-availability.

In case there is no oral agent available, or the oral agent is considered too toxic, a strategy with continuing intravenous antibiotics in an outpatient setting (OPAT) is also an option. OPAT should not be used for chronic suppressive treatment.

Table 4. Targeted antimicrobial treatment for PJI

Causative microorganism	First choice treatment	Second choice(s) of treatment in oral treatment phase	Penicillin allergy
After DAIR or 1S	R		
Methicillin-sensitive staphylococci	flucloxacillin 6 g/24h <sup>b</sup> i.v. (after loading dose 1 gram) † for 1-2 weeks + rifampicin 450 mg BID p.o.  followed by rifampicin 450 mg BID p.o. + levofloxacin 500 mg BID p.o. (levofloxacin can be replaced by ciprofloxacin 750 mg BID <sup>e</sup> po)	rifampicin 450 mg BID + clindamycin 600 mg TID or rifampicin 450 mg BID + trimethoprim- sulfamethoxazole 960 mg BID <sup>c</sup> † or clindamycin 600mg TID or rifampicin 450 mg BID + minocyclin 100 mg BD (loading dose 200mg)	cefazolin 4-6 g/24h i.v. <sup>d</sup> (after loading dose of 1 gram for 1-2 weeks instead of flucloxacillin
Methicillin-resistent staphylococci	vancomycin 35 mg/kg continuously /24 hr (20 mg/kg loading dose) OR 17.5 mg/kg BID (30 mg/kg loading dose) <sup>a</sup> for 1-2 weeks + rifampicin 450 mg BID p.o.  followed by rifampicin 450 mg BID p.o. + levofloxacin 500 mg BID p.o. (levofloxacin can be replaced by ciprofloxacin 750 mg BID <sup>e</sup> po†)	rifampicin 450 mg BID + clindamycin 600 mg TID or rifampicin 450 mg BID + trimethoprim- sulfamethoxazole 960 mg BID <sup>c</sup> or rifampicin 450 mg BID + minocyclin 100 mg BD (loading dose 200mg)	
Enterobacterales (e.g., E. coli, Klebsiella, Proteus)	ceftriaxone 2 gram OD i.v. for 1-2 weeks or cefuroxime 4.5 gram/24h i.v. for 1-2 weeks followed by ciprofloxacin 500 mg BID <sup>e</sup> p.o.	trimethoprim- sulfamethoxazole 960 mg BID p.o. <sup>c</sup>	
P. aeruginosa	ceftazidime 6 g/24hours i.v. (after loading		

C. acnes	dose 2 g) for 1-2 weeks followed by ciprofloxacin 750 mg BID <sup>e</sup> p.o.  penicillin G 6MU/24h <sup>f</sup> i.v. † (after loading dose 1MU) for 1-2 weeks  followed by		ceftriaxone 2 g 1dd i.v. †  followed by clindamycin 600 mg TID p.o.
	amoxicillin 750 mg TID p.o.  or  clindamycin 600 mg TID p.o.		
Streptococci	penicillin G 6MU † /24h <sup>f</sup> i.v. (after loading dose 1MU) for 1-2 weeks followed by amoxicillin 750 mg TID p.o. or clindamycin 600 mg TID p.o.		cefazolin 4 g/24h i.v. † (after loading dose of 1 gram for 1-2 weeks Followed by clindamycin 600 mg TID p.o.  Use ceftriaxone for viridians streptoocci/pneumococci(no breakpoints for cefazoline for this m.o.)
Enterococci - Amoxicillin susceptible	amoxicillin 6 g/24hg IV for 2 weeks,† after loading dose of 1 g.and ceftriaxone 2 gram BID for 2 weeks  or: amoxicillin 6 g/24 hr iv for two weeks † (after loading dose 1 g).  followed by amoxicillin 750 mg TID p.o.	linezolid 600 mg p.o. BID <sup>i</sup>	vancomycin 35 mg/kg continuously /24 hr (20 mg/kg loading dose) OR 17.5 mg/kg BID (30 mg/kg loading dose) for 1-2 weeks followed by linezolid 600 mg BID p.o. or continuous vancomycin iv therapy)
Enterococci - Amoxicillin resistant	vancomycin 35 mg/kg continuously /24 hr (20 mg/kg loading dose) OR 17.5 mg/kg BID (30 mg/kg loading dose) <sup>a</sup> for 2 weeks followed by linezolid 600 mg BID <sup>i</sup>	linezolid 600 mg p.o. BID <sup>i</sup>	
Anaerobes	dependent on antibiogram:  penicillin G 6MU/24hf i.v. † (after loading dose 1MU) for 1-2 weeks followed by amoxicillin 750 mg TID p.o. or clindamycin 600 mg po TID or metronidazole 500 mg TID (maximum duration of 6 weeks)^o or amoxicillin-clavulanic acid 4dd 1200 mg i.v. for 1 -2 weeks, followed by amoxicillin-clavulanic acid 3dd 875/125 mg p.o.		

1		7	ī
Candida (2 stage revision arthroplasty preferable)	fluconazole 400 mg <sup>h</sup> OD (loading dose 800 mg)		
- fluconazole susceptible			
Candida (2 stage revision arthroplasty preferable)	voriconazole 2dd 200 mg <sup>h</sup> p.o. (after loading dose of 2dd 400 mg p.o.) if susceptible or		
- fluconazole resistant	anidulafungin 100 mg OD (loading dose 200 mg) for 1-2 weeks  or an alternative echinocandin		
Culture-negative and polymicrobial PJI	discuss in multidisciplinary team		
2-stage revision	(2SR; after explantation)		
Methicillin-sensitive staphylococci	flucloxacillin 6 g/24h i.v. <sup>b</sup> † (after loading dose 1 gram) for 1-2 weeks	trimethoprim- sulfamethoxazole 960mg BID †	cefazolin 6 g/24h i.v. † (after loading dose 1 gram) for 1-2 weeks
	followed by: clindamycin 600 mg TID	flucloxacillin 1000mg 5 times daily p.o. (only if adequate absorption test)	followed by: clindamycin 600 mg TID
Methicillin-resistent staphylococci	Vancomycin 35 mg/kg continuously /24 hr i.v. (20 mg/kg loading dose) OR 17.5 mg/kg BID (30 mg/kg loading dose) <sup>a</sup> for 1-2 weeks		
	followed by clindamycin 600 mg TID p.o. or trimethoprim-sulfamethoxazole 960mg BID p.o.		
Enterobacterales and Pseudomonas	see targeted therapy for DAIR or 1SR		
C. acnes	see targeted therapy for DAIR or 1SR		
Streptococci	see targeted therapy for DAIR or 1SR		
Enterococci - Amoxicillin susceptible	amoxicillin 6g/24h <sup>g</sup> IV for 2 weeks, † after loading dose of 1 g.	linezolid 600 mg p.o. BID <sup>i</sup> maximum duration of 6 weeks#	vancomycin 35 mg/kg continuously /24 hr (20 mg/kg loading dose)
	followed by amoxicillin 750 mg TID p.o.		
Enterococci - Amoxicillin resistant	see targeted therapy for DAIR or 1SR		
Anaerobes	see targeted therapy for DAIR or 1SR		
Candida	see targeted therapy for DAIR or 1SR		
Culture-negative	discuss in multidisciplinary team		
	c suppressive treatment (starts a	after 6 weeks of	
antibiotic treatm	ent as defined under 2SR)		

pathogen	first choice	alternative	
Methicillin-sensitive staphylococci	flucloxacillin 1000 mg BID	clindamycin 600 mg BID or trimethoprim- sulfamethoxazole 960mg OD or doxycycline 100 mg OD or cephalexin 500mg 3 TID	
Methicillin-resistent staphylococci	clindamycin 600 mg BID	trimethoprim- sulfamethoxazole 960mg OD or doxycycline 100mg OD	
C. acnes	amoxicillin 500-750mg BID or clindamycin 600 mg BID		clindamycin 600 mg BID
Gram negative bacilli	trimethoprim-sulfamethoxazole 960mg OD		
Streptococci	amoxicillin 500-750mg BID	clindamycin 600 mg BID	clindamycin 600 mg BID
Enterococci - Amoxicillin susceptible	amoxicillin 750 mg BID		
Candida - Fluconazole susceptible	fluconazole 100 mg <sup>h</sup> OD		
All other organisms	discuss in multidisciplinary team		
Arthrodesis or a			
Start targeted therapy - In case of complete r - in case of partial rese			

Abbreviations: 1SR, one-staged revision; 2SR, two-staged revision; DAIR, debridement, antibiotics and implant retention; HLAR, high level aminoglycoside resistance; mg, milligram; MRSA, methicillin-resistant Staphylococcus aureus; SAT, suppressive antibiotic treatment; BID two times daily; TID three times daily; OD once daily; QID four times daily; p.o. orally; i.v. intravenously, MU million Units.

For dosing regimens for obese patients and patients with impaired renal function, see SWAB-ID: <a href="Medicatie">Medicatie</a> | SwabID (antibiotica.app)

www.eucast.org/fileadmin/src/media/PDFs/EUCAST files/Guidance documents/Cefotaxime and Ceftriaxon e for Staphylococcus aureus Infections - January 2023.pdf

<sup>e</sup> Ciprofloxacin dose range 500 mg BID - 750 mg BID for quinolone-sensitive organisms (e.g., Enterobacterales). Dose for quinolone in susceptible with increased exposure organisms (I) (e.g., *S. aureus* and *Pseudomonas* spp): 750 mg BID

<sup>f</sup> Penicillin G range 6-12 MU/24h i.v. (in case of 12 MU, loading dose 2MU)

<sup>&</sup>lt;sup>a</sup> For therapeutic drug monitoring (TDM) of vancomycin we refer to SWAB-ID: <u>TDM - vancomycine | SwabID (antibiotica.app)</u>.

<sup>&</sup>lt;sup>b</sup>Flucloxacillin dose range 6-12 g/24 hr (in case of 12 g/24, loading dose 2 g)

<sup>&</sup>lt;sup>c</sup>Trimethoprim-sulfamethoxazole (co-trimoxazole) dose range 960 mg BID - 960 mg TID

<sup>&</sup>lt;sup>d</sup> Cefazolin range 4-6g/24 hr, based on

g Amoxicillin range 6-12 g/24 hr (in case of 12 g/24, loading dose 2 g)

<sup>&</sup>lt;sup>h</sup> Fluconazol, voriconazole: check levels in blood for potential dosage adjustments

<sup>&</sup>lt;sup>i</sup>Frequent control of liver enzymes, blood count and creatine kinase is indicated if linezolid is used for a longer time.

# Part III: literature review and formulated recommendations

## 1. General principles of antimicrobial treatment of PJI

PJIs are complex, heterogeneous complications and almost always require both surgical intervention and prolonged antimicrobial therapy. Therefore, one of the pillars in the care of patients with a PJI is strong collaboration between all involved medical and surgical specialists (e.g., infectious disease specialist, medical microbiologist, pharmacist, orthopaedic surgeon, plastic surgeon and trauma surgeon). Since not all medical institutions in the Netherlands will have the necessary resources to assure proper collaboration and implementation of guidelines, approachable contact with specialty centres with the option of referral is highly recommended. It is also recommended to implement a multidisciplinary team consisting of orthopedic surgeons, infectiologists and/or microbiologists to discuss the management of patients with PJI on a regular base.

The clinical criteria for diagnosing a PJI has been published by the European Bone and Joint Infection Society (EBJIS). PJI should be suspected in all patients with persistent wound drainage after arthroplasty, ongoing or acute onset of a painful prosthesis, or with a history of wound healing problems or infection.[3-6, 8] After a thorough history and physical examination, other modalities like serum biomarkers (C-reactive protein), synovial fluid analysis(culture, leucocyte count, leukocyte differential, Alpha defensin), histology, or radiology (plain radiographs) might be used to diagnose PJI.[3-6, 8] Blood cultures should be obtained when fever is present or if the patient has a concomitant infection with a pathogen that might spread to the prosthesis (e.g., *S. aureus*). In addition, intraoperative histopathological and microbiological examination of tissue samples is needed, preferably without prior antibiotic treatment (especially in revisions with high suspicion for PJI and preoperative negative cultures).[3-6, 8] A combination of multiple intraoperative cultures increases the yield of microorganisms and reduces the chance of incorrectly treating contaminants.[14-18].

In most practical guidelines treatment strategies are based on the differentiation of acute versus chronic infections. The definition of acute and chronic PJI differs across guidelines and can be related to the duration of symptoms or the time evolved since the arthroplasty. Most guidelines use a symptom duration of 3 weeks as a cut-off point [3, 4] while others use 6 weeks [6], or separate a post-surgery group (up to three months after placement of the prosthesis) into an early acute postoperative (0 to 3 wks) and an early chronic postoperative period (3 weeks to 3 months). In this guideline, PJIs are divided into early acute (postoperative), late acute (hematogenous) and late chronic PJIs, as defined in the Abbreviation Table. In acute PJI, a DAIR with implant retention is often performed while chronic infections usually result in one- or two stage revisions. In rare cases, amputations or suppressive therapy with implant retention is needed. Some guidelines have different treatment recommendations for one- and two-stage procedures with non-identical empirical regimens or treatment durations.

## **Recommendation:**

We recommend administering antibiotic therapy for PJI initially by the parenteral route. We recommend continuous infusion, in particular for betalactam antibiotics. An early switch to oral therapy (after one week of IV treatment) is recommended if the patient is clinically improving, has decreasing inflammatory parameters, has no contraindications to oral therapy and if there is an appropriate oral agent available with adequate bio-availability.

Good practice statement

#### Rationale:

Many of the antibiotics that are recommended in this guideline can be administered intravenously, intermittently or by continuous infusion. To our knowledge, there are no studies comparing both infusion methods in PJI (although we did not perform a systematic literature review based on a clinical question). The guideline committee prefers administration with continuous infusion for antibiotics with time-dependent killing (i.e. most betalactam antibiotics) where possible, assuring an effective concentration at all times and allowing drug monitoring when needed. Traditionally PJI is treated with intravenous antibiotics in order to obtain the minimum inhibitory concentration as fast as possible. Once there is clinical improvement, most IV antibiotic regimens can be switched to oral regimens.[19-21] Switching to an oral regimen for sensitive pathogens reduces the risks of vascular access, creates the possibility of home-based therapy and lowers the financial burden. No literature to date supports the use of only oral antibiotic therapy although the IDSA guidelines suggest that pathogen-specific, highly bioavailable oral therapy (fluoroquinolones/linezolid) may be an alternative as initial therapy for some PJI cases.[3] The suggested dosages for both empiric and targeted antibiotic regimens are historically based and need to be adjusted to drug clearance, usually by adjusting to creatinine clearance, weight or liver function, and need to be adjusted to accommodate drug-drug interactions.

## 2. Allergies to first choice antibiotics and toxicity

#### **Recommendation:**

We recommend to consult the SWAB guideline 'Approach to suspected antibiotic allergy' in case of a suspected antimicrobial allergy, for detailed information regarding the approach to (suspected) antibiotic allergies, and potential cross-reactivity of antibiotics.[13] Good practice statement

## Rationale:

Reported allergies to first choice antibiotics, such as penicillins, are fairly common; Although, in practice, only a small proportion of reported allergies are true and clinically relevant allergies.[13] Thorough medical history and a detailed search in the electronic patient file can provide more insight into whether a patient has a true allergy and, if this is the case, into its severity. In general, first choice antibiotics are preferred, as they are advised because they are more effective against the causing microorganisms, cheaper, less toxic or better available than alternative antibiotics.

Alternative antibiotics should only be used in selected circumstances to decrease antibiotic overuse and to prevent occurrence of antimicrobial resistance. For these reasons, only in case of true and clinically significant allergy or toxicity, an alternative of the first choice antibiotic should be chosen. Furthermore, in these cases consultation of an allergist, immunologist or dermatologist is advised as drug challenge (e.g., to test for cross-reactivity) or drug desensitisation may be an option. For detailed information regarding the approach for (suspected) antibiotic allergies and cross reactivity we refer to the corresponding SWAB guideline: "The Dutch Working Party on Antibiotic Policy (SWAB) guideline for the approach to suspected Antibiotic Allergy".[13]

## 3. General principles of surgical treatment

Although beyond the scope of the present guideline, the following paragraphs contains some guidance on surgical principles for PJI. For details on surgical strategy and surgical techniques, we would like to refer to the Dutch orthopaedic guidelines.[6]

In case of early acute or late acute PJI a DAIR procedure is indicated: debridement, antibiotics and implant retention. This surgical treatment typically consists of open deep debridement and thorough irrigation, using 6 litres of saline administered by low-pressure pulsatile jet lavage. Whenever possible, modular components should be exchanged as it offers a better potential for thorough debridement and irrigation and mechanical removal of the biofilm. Moreover, modular component exchange is advised because the polyethylene component (acetabular liner or tibial inlay) may be colonised by microorganisms and removal provides space for rigorous cleaning. The soft tissue should be meticulously closed in a multilayer fashion.

In chronic PJI, there is no consensus on whether 1SR (one-staged revision) or 2SR (two-staged revision) is the preferable surgical procedure. In 1SR all components are exchanged at once and replaced by a new prosthesis, whilst during a 2SR a spacer is placed after removal and a second surgery is performed after 3-6 weeks to 6 months depending on team preferences and soft tissue conditions. No evidence for timing and procedure is available. If the identified micro-organism is susceptible to oral antibiotics and the soft tissues provide adequate coverage of the joint, a, one stage can be a good option to provide safe and effective treatment.

Administration of prophylactic antimicrobial treatment (usually cefazolin) in all cases is advised prior to incision. Various tissue samples for bacterial cultures are obtained, preferably 5-6 samples to increase detection of microorganisms. Each tissue sample is obtained using a clean instrument to avoid contamination. Swabs are not advised, not from tissue and not from draining fistulae. Tissue samples should be cultured for up to 14 days. Empirical antimicrobial treatment should be adjusted based on cultures. Gram-negative coverage can be stopped if cultures do not reveal Gram-negative microorganisms after 2-3 days. [22]

## 4. Empirical therapy

## **Recommendation:**

We suggest to select an empirical therapy for treating a PJI based on the suspected causative pathogens and the surgical treatment that is performed. The prescriber should take into consideration previous culture results, previous treatments and the type of surgery (which is often based on the chronicity of the infection (i.e. early acute postoperative, late acute (hematogenous) or late chronic infection (Table 3).

Good practice statement

## **Recommendation:**

In case of a DAIR for an early acute postoperative infection, we suggest to empirically treat with vancomycin and ceftriaxone to cover Staphylococcus aureus, streptococci, coagulase negative staphylococci (CNS), enterococci and Enterobacterales. We do not recommend to empirically cover *Pseudomonas* (unless local epidemiology indicates a high prevalence). Empirical treatment should be adjusted based on the clinical circumstance, e.g., already known cultures from earlier PJI in the same joint or wound colonisation with multiresistant micro-organisms. The suggestion for empirical treatment with vancomycin is based on the high prevalence of both CNS and enterococci in >10% of early postoperative PJI in 2 Dutch regions (unpublished data) (Table 3). Good practice statement

## **Recommendation:**

In case of a DAIR for a late acute (haematogenous) infection, we suggest to treat empirically with flucloxacillin to cover *Staphylococcus aureus* and streptococci. We suggest to add ceftriaxone if the

patient has a concurrent clinical presentation that is associated with Enterobacterales, like cholangitis or urosepsis (Table 3).

Good practice statement

#### **Recommendation:**

In case of a one-stage revision (1SR) for a late chronic infection we advise to give targeted treatment based on cultures. This is because a 1SR is generally only performed in patients with known causative pathogens. If, however cultures are not yet known, we suggest to treat empirically with vancomycin to cover CNS, enterococci and *Cutibacterium acnes* (Table 3). Good practice statement

## **Recommendation:**

In case of a two-stage revision (2SR) we advise to give targeted treatment after explantation of the prosthesis, based on cultures. This is because a 2SR is mostly performed in patients with already known causative pathogens and there is no prosthesis left or implanted for which immediate postoperative coverage with broad-spectrum antibiotics is warranted (Table 3). Good practice statement

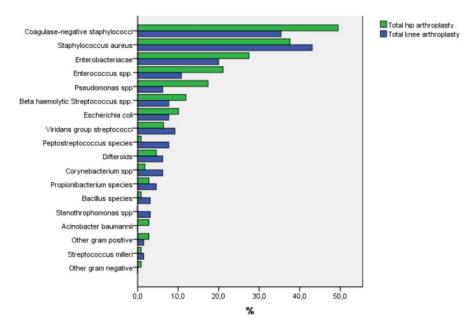
#### Rationale

The IDSA guideline provides pathogen specific recommendations that take into consideration the surgical strategy of choice, but provides no recommendations on empirical therapy.[3] We decided not to perform a systematic literature search for this topic, because of lacking evidence and differences in empirical treatment in the Netherlands based on local susceptibility patterns. To give a practical guidance for clinicians, Table 3 shows an overview of recommended empirical antimicrobial treatment regimens for PJI, to be started after surgical debridement with intraoperative cultures.

Empirical antimicrobial treatment should be directed at the most frequently isolated pathogens of PJI. This is especially important in case of DAIR and 1SR to treat remaining bacteria after debridement, and to prevent new biofilm formation of surviving bacteria on the debrided or newly inserted implant. As a result, empirical antibiotic therapy in case of DAIR or1SR has a broad spectrum. In case of 2SR, the causative pathogen is usually already known prior to the explantation and targeted antibiotic treatment can be started postoperatively. If the causative pathogen is not known prior to surgery, then empirical broadspectrum treatment is not needed because the foreign material is taken out, making new biofilm formation less of an issue. In these cases less virulent micro-organisms do not need to be covered empirically. r.

With respect to the causative micro-organisms, most PJIs are caused by CNS (30-41%) and methicillin-sensitive Staphylococcus aureus (MSSA, 12–47%). Streptococcus spp. and Enterococcus spp. are less common causes, as are gram-negative bacteria such as Escherichia coli and Pseudomonas aeruginosa (4-7%).[23-26] Methicillin-resistant Staphylococcus aureus (MRSA) and anaerobes are rarely isolated, especially not in Northern Europe. Polymicrobial cultures often occur in early postoperative infections or (chronic) infections in the presence of a sinus tract, and need to be taken into consideration when choosing an empirical strategy. In Europe A recent retrospective study in the Netherlands exploring the empirical treatment of acute PJI [27], reported MSSA in 50% of included patients, CNS in 19% of patients and group A/B haemolytic streptococci in 16%. No multiresistant organisms were found in this study and multiple microorganisms were found in 37% of patients.[27] In a larger cohort study in two community hospitals in the Netherlands the most common microorganisms associated with PJI after total hip replacement and knee replacement were CNS (49.5% and 35.4% respectively) and S. aureus (37.6% and 43.1% respectively), as can be seen in Figure 1.[28]. Further, in two Dutch regions, the prevalence of CNS and enterococci in early postoperative PJI was >10% (unpublished data), indicating that low-virulent pathogens, usually associated with more chronic infections are significantly involved in early postoperative PJI, which is

the reason that empirical vancomycin is suggested for early postoperative PJI after DIAR or 1-SR., he exact local resistance rates of gram-negative isolates to cephalosporins in PJI isolates in the Netherlands are not known. Dutch studies report a much lower rate than in the mentioned European studies.[27, 28] In a Dutch study analysing the causative pathogens in acute PJIs after revision surgery, the incidence of Pseudomonas was 10%, while in another Dutch study performed within the NINJA network including mainly primary arthroplasties, the incidence of Pseudomonas species was 5%. These differences indicate either differences in local epidemiology or the studies population (primary versus revision). Therefore, we only recommend to include Pseudomonas coverage in the empirical treatment of early acute PJIs, if local epidemiology dictates to do so.



Percentage micro organisms associated with PJI in THA and TKA.

Figure 1: microorganisms associated with PJI in total hip and total knee arthroplasties. Copied from de Vries et al.[28]

## 5. Culture-directed antimicrobial therapy

Several studies have reported that microorganism-directed oral antibiotics following an initial intravenous regimen or reimplementation, reduces the risk of failure to further infection significantly.[29-31] However, in Dutch practice local guidelines regarding recommended antibiotics per microorganisms vary greatly. For this reason, we systematically reviewed and appraised the evidence on the optimal treatment strategy for several microorganisms. Recommendations for targeted therapy are summarised in Table 4.

## Staphylococci

PICO 1a: In a person with a PJI caused by staphylococci, is a rifampicin-based regimen more effective in achieving clinical cure?

## **Recommendation:**

We suggest to add rifampicin in the treatment of (rifampicin-susceptible) staphylococcal PJI treated with DAIR or 1SR

Strength of recommendation: conditional, quality of evidence: low

#### Rationale:

Rifampicin is a strongly bactericidal agent against staphylococci with good bone penetration and excellent efficacy against bacteria within biofilm, making it an attractive drug to use for PJI. However, the clinical superiority of rifampicin compared to other drugs is still unclear. Therefore a search was conducted to critically appraise the relevant literature regarding this topic.

11 studies were included in the evidence tables in Appendix C in which rifampicin combination regimens for staphylococcal PJI were compared with non-rifampicin combinations. In a high quality multicenter randomised controlled trial by Karlsen et al. on 38 *S. aureus* PJI's of hip and knee treated with DAIR, no significantly better cure rate was found in patient subsequently treated with 6 weeks of rifampicin combination compared with standard treatment (cloxacillin and/or vancomycin, and gentamicin sponges).[32]

Ascioni et al. found a significant better cure rate for rifampicin compared to no rifampicin for treatment of staphylococcal hip/knee PJI in a group of patients treated with either DAIR/2SR or antibiotic suppression.[33] However, this could not be confirmed in a selected group of patients treated only with 2SR.[34]

A retrospective cohort study of Senneville et al. on 98 patients treated with DAIR/1SR/2SR/resection/arthrodesis for *S. aureus* PJI (hip/knee) showed a cure rate of 75% versus 63% (p=0.002) for rifampicin-based treatment versus other combinations respectively.[35]

A retrospective observational study of Becker et al. on a combined group of 79 patients treated with DAIR (hip/knee) for either S aureus or coagulase negative staphylococci (CNS). Cure rates did not significantly improve by a rifampicin based therapy versus other antibiotics.[36] An earlier study of Drancourt et al on a combined group of *S. aureus* and CNS in prosthesis 1SR, 2SR or osteosynthetic implant removal did not show a significant better cure rate when rifampicin was added to either fusidic acid or ofloxacin for 6-9 months.[37]

A register study by Holmberg et al on *S. aureus* and CNS knee PJI (based on culture and purulence) showed a significantly better cure rate of 81% versus 47% (p=0.01) when rifampicin compared to other antibiotics.[38]

A retrospective multicenter cohort study of Lesens et al studied the efficacy of rifampicin in treatment of *S. aureus* PJI with DAIR of hip and knee in 137 patients.[39] A positive effect was seen when rifampicin was added to other antibiotics, but only when the treatment was complete (i.e., >3 weeks): In these cases the unadjusted Hazard Risk for failure (including chronic suppression) was 0.08 [0.018–0.36] p = 0.001. The empirical optimal cut-point for duration of rifampicin based on ROC curve was 10.5 weeks.

The study of Lora-Tamayo et al was a retrospective multicenter observational study on treatment of S. aureus PJI of hip, knee and other joints with DAIR.[40] Of the 345 patients, 303 received rifampicin combined with other antibiotics. Some risk of bias resulted from e.g., lack of information on control and intervention groups and 5% lost to follow up. Overall 47 subjects out of 284 failed treatment with >30 days of rifampicin. The adjusted Hazard Ratio was 0.49 (0.26–0.91) p=0.024, suggesting that there is a protective effect of rifampicin.

Tornero et al performed a retrospective analysis on a prospective cohort study on PJI of hip and knee treated with DAIR/1-2 stage/resection/arthrodesis.[41] Of the 143 DAIR cases, 92 involved gram positive organisms, 53 (37.1%) of which were *S. aureus*. In gram-positive infections, rifampicin and linezolid, trimethoprim-sulfamethoxazole (co-trimoxazole) or clindamycin combinations had a higher failure rate (27.8%, P = 0.026) than rifampicin in combination with levofloxacin, ciprofloxacin or amoxicillin (8.3%) or monotherapy linezolid/ trimethoprim-sulfamethoxazole (0%).[41]

Recently, two systematic reviews and meta- analysis analysed all studies evaluating outcome for staphylococcal PJI after DAIR. All studies described above were included in these reviews. Both reviews found that rifampicin-based strategies were not superior to non-rifampicin strategies.[42, 43] The RCT of Zimmerli et al was excluded from these reviews due to the low patient number (18 patients with PJI, of whom only eight patients received rifampicin).[44] Further, outcome was not stratified for type of infection (both fracture-related infections and PJI were included). In this trial patients were randomised between rifampicin combination therapy and ciprofloxacin monotherapy. Intention-to-treat analysis showed a nonsignificant 89% versus 60% cure rate in favour of rifampicin; significance was reached in the per-protocol analysis. However, the choice for ciprofloxacin monotherapy in the control arm, nowadays regarded as inferior therapy for staphylococcal PJI, resulted in four of five failures in this group due to ciprofloxacin resistance. The RCT of Karlsen et al contained 3 times as many patients as the trial of Zimmerli et al and had a different comparator arm (beta-lactams instead of ciprofloxacin). In this study the additional use of rifampicin was not associated with improved outcome but this study was also underpowered.[32]

A retrospective cohort study found that moxifloxacin is an alternative quinolone to levofloxacin or ciprofloxacin with favourable effects. [45] In this study, the success rate of a group of patients treated with levofloxacin/rifampicin was 89.0% versus 87.5% in those treated with moxifloxacin/rifampicin combination (p>0.5).

In most studies discussed above, rifampicin-based regimens were compared with non-rifampicin based regimens making specific comparison of rifampicin with other targeted antibiotic regimens difficult. In a recent study with 200 patients with staphylococcal PJI, which was published after the literature review, a rifampicin-based strategy was compared specifically with flucloxacillin and clindamycin and only 5 days of rifampicin induction therapy. Treatment with clindamycin or flucloxacillin monotherapy resulted in similar outcomes compared to long-term rifampicin combination treatment. Therefore, these regimens can be considered if rifampicin is not an option. Due to the high oral dose of flucloxacillin in this study (4-5 dd 1000mg) and the need for testing of oral absorption before start, this is not used in many centers and therefore not generally recommended in this guideline although it can be used.[46]

Summary of evidence: From the included cohort studies and systematic reviews and meta-analyses, there is no clear superiority of rifampicin combination therapy over other treatment regimens for staphylococcal PJI. However, studies regarding other specific antimicrobial regimens are very limited and reported outcome of patients treated with rifampicin combination therapy is usually good. The efficacy of rifampicin in these studies was often studied in a combination of different treatment regimens (DAIR/1SR/2SR/other), arthroplasties (hip/knee/other) and microorganisms (S aureus/CNS/other). Rifampicin does have (gastro-intestinal) side effects and drug-drug interactions which can limit the applicability of the drug. Rifampicin reduces serum concentrations of cotrimoxazole, doxycycline, clindamycin and moxifloxacin but we found no studies in which this was associated with higher rates of treatment failure if treated with adequate dosages of antibiotics. The quality of evidence is reduced to lowbased on the inconsistency of outcomes in the 2 RCTs and the retrospective studies. The recommendation is therefore conditional. Currently, most centres in the Netherlands use rifampicin-based antibiotic therapy for PJI. We suggest using rifampicin, but in case of side effects, other contra-indications and drug-drug interactions, it is valid to withhold rifampicin.

PICO 1b: In a person with a PJI caused by staphylococci, is a non-fluoroquinolone combined with rifampicin as effective as a fluoroquinolone combined with rifampicin in achieving clinical cure?

## **Recommendation:**

We suggest, if rifampicin is used for staphylococcal infection, to combine it with a fluoroquinolone (in the absence of resistance to fluoroquinolones or rifampicin) in PJI.

Strength of recommendation: conditional, quality of evidence: low

#### Rationale:

We identified one trial that compared treatment outcomes of orthopaedic infections treated with fluoroquinolone and rifampicin with those treated with a non-fluoroquinolone antibiotic (i.e., fusidic acid) and rifampicin in 42 patients. [47] This trial reported similar efficacy and safety of subjects with orthopaedic implants treated with rifampicin combined with either fusidic acid or ofloxacin with a 1-year follow-up. [47] Limitations of this study are its small sample size and the fact that this study was not specific for PJI (but also includes other orthopaedic implant infections); Moreover, this study was conducted more than twenty years ago which means that antimicrobial resistance data and health care systems (and thereby treatment outcomes) might be different presently.

Three other more recent but retrospective studies found that rifampicin combined with a fluoroquinolone (as opposed to rifampicin with another type of antibiotic) was associated with less (late) treatment failures in subjects with PJI who underwent DAIR.[36, 39, 40] However, in one study this association was not significant in multivariate analysis.[36] Another retrospective study also found that rifampicin-fluoroquinolone combination therapy was independently associated with better treatment outcomes; however, this treatment combination was compared to both other rifampicin-combination and non-rifampicin antibiotic therapies.[35]

Summary of evidence: evidence from one small RCT suggested that rifampicin with non-fluoroquinolone combinations in the orale treatment phase leads to similar clinical outcomes as rifampicin with fluoroquinolones. The RCT is likely to have been underpowered to demonstrate a difference. Four retrospective studies, suggested that rifampicin and quinolone combination does lead to better outcomes than other combinations. There is therefore imprecision and inconsistency in the reported studies. The need for a more restricted use of fluoroquinolones should also be taken into account. The most important reason to suggest to use fluoroquinolones as co-drug with rifampicin is that this is reported in most studies, while there is ample evidence for other combination strategies. Of note, in case of fluoroquinolone-resistant staphylococci, an alternative codrug needs to be given to prevent rifampicin monotherapy. The committee chose to lower the evidence to low. The strength of the recommendation is conditional.

PICO 1c: In a person with a PJI caused by methicillin resistant coagulase negative staphylococci, is initial treatment with daptomycin as effective as vancomycin in achieving clinical cure?

## **Recommendation:**

We suggest to use vancomycin, not daptomycin, as first choice of treatment for PJI caused by methicillin resistant staphylococci.

Strength of recommendation: conditional, quality of evidence: very low

#### Rationale:

In *In-vitro* and in animal studies, daptomycin has been shown to be more effective than vancomycin for the treatment of experimental foreign-body infections by biofilm forming *methicillin resistant staphylococcus aureus* (MRSA).[48] However, daptomycin has the disadvantages of higher costs and rare but serious side effects; Moreover, better efficacy of daptomycin compared with vancomycin in PJI caused by *staphylococci* in humans is not known. For this reason, we conducted a search for studies comparing clinical outcomes in humans between daptomycin and vancomycin for the treatment of PJI caused by *Staphylococci*. However, literature search yielded no relevant studies to draw conclusions on this topic. One randomised controlled trial by Byren et al. investigated the effect of daptomycin but this study was excluded because it was not powered to detect statistical differences or demonstrate non-inferiority of daptomycin versus standard-care-therapy (most often vancomycin).[49] One systematic review only contained the Byren study.[50]

### Summary of evidence:

There is insufficient evidence to support daptomycin over vancomycin in methicillin-resistant staphylococci. There is, however, much more experience with vancomycin in clinics in the Netherlands where it is frequently used for other indications than PJI. Given the risk of rare but serious side effects, the higher costs for daptomycin and the relative inexperience with daptomycin in the Netherlands, and the fact that often an early switch to oral antibiotics is possible, we suggest to use vancomycin rather than daptomycin for the treatment of PJI caused by methicillin resistant staphylococci.

## Streptococci

PICO 2a: In a person with a PJI caused by streptococci, is a rifampicin-based regimen more effective in achieving clinical cure than treatment regimens without rifampicin?

## **Recommendation:**

We suggest not to use rifampicin for streptococcal PJI.

Strength of recommendation: conditional, quality of evidence: low

## Rationale:

Streptococci are estimated to be the causative microorganisms in around 10% of PJI cases. [28] PJI caused by streptococci most often originates from a distant focus through hematogenous spread. Clinically, a distinction can be made between PJI caused by highly virulent beta-hemolytic streptococci causing acute PJI and chronic PJI caused by low virulent viridans streptococci.

A recent study found that in twenty-five studies, the outcome of acute streptococcal PJI treated with DAIR was reported. [51] The pooled success rate was 70% (95% CI 64%-76%). Of those, four retrospective studies specifically addressed the role of rifampicin. In the study of Mahieu et al., most patients received combination therapy including a  $\beta$ -lactam (mainly amoxicillin) with rifampicin or levofloxacin.[52] In this study, no antimicrobial therapy, alone or in combination, was associated with a better outcome. rifampicin—levofloxacin combination was not independently associated with higher cure rates in the study by Fiaux et al..[53] In the study conducted by Wouthuyzen-Bakker et al. in late acute (hematogenous) PJI, failure rate was 22.7% (5/22) when rifampicin was added versus 42.5% (31/73) when rifampicin was not added to the antibiotic regimen of streptococcal PJI (p 0.13).[54] The largest study on streptococcal PJIs also failed to show a benefit of rifampicin

therapy.[55] Interestingly, in this last study rifampicin did improve the prognosis of patients who were treated with a  $\beta$ -lactam (compared with those treated with glycopeptides for example). This may be due to confounding by indication (e.g., more polymicrobial PJI with enterococci or coagulasenegative staphylococci in patients treated with glycopeptides), but this was not separately analysed.

The pooled risk ratio for the effectiveness of rifampicin in these studies was 1.31 (95%CI 0.97-1.78). A recent systematic review by Aydin et al.[43] found higher RR for success when rifampicin was used (1.78 (1.15-2.76), but they did not analyse the most recent study of Wouthuyzen-Bakker.[54] All studies were retrospective observational studies and were inherently hampered by selection bias, immortal time bias and confounding by indication.

No stratification was performed for several types of antibiotic strategies like amoxicillin, penicillin or clindamycin. Further, the dosage of the used antibiotics was not mentioned in the studies. Failure of treatment for streptococcal may be related to the virulence of *Streptococci* leading to more local necrosis and inflammation, eventually resulting in more failures and revision surgery compared with other pathogens. In one study, *S. agalactiae* (n=27/70, 39% of cases) as the infecting organism (OR 7.09, 95% CI 1.58–31.8; adjusted p = 0.0334) was an independent predictor of relapse.[52] However, in another study, virulent streptococci were not associated with a worse outcome.[55] In all other studies, outcome was not stratified for low-virulent or high-virulent streptococci.

The absence of evidence for rifampicin in clinical studies may relate to the excellent bactericidal activity of penicillin against *Streptococci*. However, a high-quality RCT is needed to definitely determine the role of rifampicin for streptococcal PJI.

## Summary of evidence:

Four retrospective observational studies were identified that compared patients with and without treatment with rifampicin in streptococcal PJI. The studies were hampered by selection bias, immortal time bias and confounding by indication. Details, e.g., on dosage and timing were not available. The evidence was reduced to low. The advantages of a possible benefit currently do not outweigh the disadvantages of more toxicity and drug-drug interactions which are associated with the use of rifampicin and fluoroquinolones. The strength of recommendation is conditional.

PICO 2b: In a person with a PJI caused by streptococci, is oral treatment with amoxicillin as effective as clindamycin in achieving clinical cure?

## **Recommendation:**

We suggest to use amoxicillin for oral treatment of streptococcal PJI. Strength of recommendation: conditional, quality of evidence: very low

## Rationale:

The literature screened for this guideline does not contain prospective head-to-head comparisons of different antimicrobial treatment strategies for streptococcal PJI. The largest included study reported outcomes of streptococcal PJI treated with rifampicin (n=116, failure 28%), beta lactams (n= 270 of which 206 beta lactam monotherapy; failure 32%), glycopeptides (n=29, failure 55%) and trimethoprim-sulfamethoxazole (n=9, failure 67%). In this study, clindamycin monotherapy was also used in 30 patients but outcome for this subgroup was not reported.[55] In one smaller study [56], amoxicillin was always combined with a second antibiotic. In the study by Fiaux et al.,[53] failure rate on treatment with clindamycin (n=2) and amoxicillin (n=14) was 50%. Based on the size and quality of the studies, adequate comparison of both regimens is not possible.

## Summary of evidence:

There does not seem to be a difference in outcome between beta lactam and clindamycin therapy for streptococcal PJI, but there are no head-to-head comparisons between both types of antibiotics. There is ample experience with both types of antibiotics in the Netherlands. Both are cheap and are readily available. The quality of available evidence is reduced from low (with retrospective study) to very low given the indirectness of the comparison. According to the expert group, both amoxicillin and clindamycin can be used to treat streptococcal PJI. We advise basing the choice for a particular regimen on antibiotic susceptibility, tolerance to antibiotics and patient feasibility. Amoxicillin has a different antibacterial spectrum compared with clindamycin but is associated with more drug (gastro-intestinal) side effects and drug hypersensitivity. Clindamycin is associated with more damage to the microbiome, possibly resulting in *Clostridioides difficile* associated diarrhoea. Both antibiotics are used as treatment for other bone and joint infections and are relatively cheap. Given the increasing prevalence of antimicrobial resistance to clindamycin, and the lesser effect on (anaerobe) flora, it seems valid to prefer use of amoxicillin for streptococcal PJI. Clindamycin is a reasonable alternative treatment. The strength of the recommendation is conditional.

## Enterococci

PICO 3: In a person with a PJI caused by enterococci, is initial treatment with monotherapy as effective as a combination therapy in achieving clinical cure?

## **Recommendation:**

We suggest to treat patients with enterococcal PJI sensitive to amoxicillin either with combination therapy with amoxicillin and ceftriaxone, or with amoxicillin monotherapy.

Strength of recommendation: conditional, quality of evidence: low

## **Recommendation:**

We suggest to treat patients with amoxicillin-resistant enterococcal PJI with vancomycin monotherapy

Strength of recommendation: conditional, quality of evidence: low

#### Rationale:

Only retrospective observational studies evaluating the efficacy of antibiotic combination treatment for enterococcal PJI have been identified. These studies report conflicting results. Some studies observed no superiority of monotherapy versus combination therapy,[57-60] while another study reports superior results using combination treatment.[61] These differences may be due to bias by indication in which the more severe cases are often treated with combination therapy leading to an underestimation of its efficacy. Alternatives as 'add on' antimicrobials reported in literature are rifampicin, daptomycin and fosfomycin.[59, 62, 63]

## Summary of evidence:

Most retrospective studies found no difference in outcome between combination therapy and monotherapy for enterococcal PJI. There is considerable chance of bias due to indication in these studies which might have led to the absence of effect in the combination therapy group. There is inconsistency in the results. The quality of evidence is therefore reduced from moderate to low.

In prosthetic heart valve endocarditis, guidelines suggest treating with combination therapy in case of enterococcal endocarditis. Considering the biofilm producing ability of enterococci, the high failure rate of enterococcal PJI reported in literature and the subsequent major consequences for the patient, we suggest combination therapy for amoxicillin-sensitive enterococci if the implant is debrided and retained, at least during the first two weeks of antibiotic treatment. However, there are disadvantages of double therapy; the therapy needs to be given parenterally, there are higher costs associated with therapy and double therapy is likely to have more damaging effects to the microbiome than monotherapy. In combination with the low quality of evidence, the panel therefore also considers monotherapy with amoxicillin an comparable alternative to combination therapy for amoxicillin-sensitive enterococcal PJI. The recommended second antimicrobial of choice according to the expert panel is ceftriaxone in amoxicillin susceptible enterococci.[64] In amoxicillin-resistant enterococci, there are no high-quality studies that suggest that vancomycin/gentamicin combination therapy leads to better outcomes, although it is recommended in endocarditis. Double therapy of a glycopeptide and an aminoglycoside often leads to nephrotoxicity and ototoxicity, needs to be given intravenously, has more damaging effects on the microbiome, and will cost more than vancomycin monotherapy. Alternatives as 'add on' antimicrobials reported in literature are daptomycin and fosfomycin. Linezolid could be used as an oral alternative based on efficacy in-vitro and in other infections.[58] Tedizolid, which appears to have fewer side effects and interactions than linezolid, is currently not available in the Netherlands. These antimicrobials may be considered in case of side effects or allergy to the first line treatment. The strength of recommendation given the low quality of evidence is conditional.

## **Gram-negative bacilli**

PICO 4: In a person with a PJI caused by gram-negative bacilli, is oral treatment with a trimethoprim/sulfamethoxazole as effective as oral treatment with a fluoroquinolone in achieving clinical cure?

## **Recommendation:**

We recommend to use a fluoroquinolone over trimethoprim-sulfamethoxazole in treatment of PJI caused by gram negative bacilli.

Strength of recommendation: conditional, quality of evidence: very low

## Rationale:

Fluoroquinolones are classically considered as the most potent anti-biofilm antibiotic for gramnegative bacilli. This is mostly based on *in vitro* data in which fluoroquinolones show the highest biofilm eradication rate when compared to other antibiotics.[65-67] In addition, observational studies demonstrated a higher failure rate of gram-negative PJIs when patients were not treated with a fluoroquinolone. The largest study has been performed by Rodriguez-Pardo, a multicentre retrospective observational study from Spain including 139 patients.[68] The success rate of patients treated with ciprofloxacin (n=124) in ciprofloxacin-susceptible strains was 79% compared with 40% when patients were treated with other antibiotics (n=15) (P 0.001), and the use of ciprofloxacin was an independent predictor or treatment success in the total cohort (aHR 0.23, 95% CI 0.13 – 0.40). However, the non-ciprofloxacin group was small (n=15) and baseline characteristics of the two groups were not reported which hampers an adequate comparison. Another smaller study (n=47) confirmed better outcomes of patients treated with ciprofloxacin compared to those treated with other antibiotics but in this study the non-ciprofloxacin group consisted of many patients with ciprofloxacin-resistant strains for which ciprofloxacin was not indicated at al.[69] In addition, two observational studies report excellent outcomes when a fluoroquinolone is part of the antibiotic regimen.

Fluoroquinolones were used in 15 cases (28%) in one of the studies but the outcome was not reported for the patients treated with fluoroquinolones. The other study was a case series of 17 patients.[70, 71] No studies have directly compared the efficacy of trimethoprim-sulfamethoxazole with a fluoroquinolone. The only direct comparison that has been made between an oral fluoroquinolone and an alternative regimen is with intravenous beta-lactams.[72] In this study, patients who could not be treated with a fluoroquinolone remained on IV beta-lactams during the whole treatment period with or without another co-antibiotic. Clinical outcomes between both groups were similar.

## Summary of evidence:

Outcomes with fluoroquinolones were better than those with other oral antibiotic regimens in preclinical and retrospective clinical studies, although no direct comparison has been made between fluoroquinolones and trimethoprim sulfamethoxazole. The effect was large in most studies. There was no large inconsistency or impreciseness or indirectness. The quality of evidence was very low. Considering the large effect on outcome, the consistency with pre-clinical studies but the very low evidence, the recommendation is conditional.

## Cutibacterium (Propionibacterium) acnes

PICO 5a: In a person with a PJI caused by *Cutibacterium (Propionibacterium) acnes*, is oral treatment with amoxicillin as effective as oral treatment with clindamycin in achieving clinical cure?

## **Recommendation:**

We suggest to treat *Cutibacterium acnes* PJI with amoxicillin in the oral treatment phase.

Strength of recommendation: conditional, quality of evidence: very low

## Rationale:

Literature search yielded no studies comparing clinical outcomes of treatment with amoxicillin and clindamycin for PJI caused by *Cutibacterium acnes* (or other species e.g., *C. avidum* and *C. granulosum*). Therefore, it is currently not known if amoxicillin is as effective as clindamycin as oral treatment for PJI caused by *C. acnes*. For this reason, determination of preferred antibiotic is based on data regarding *in vitro* susceptibilities, oral bioavailability, bone penetration, side effects and costs. A European surveillance study in 2004 showed increase of prevalence of resistance of *C. acnes* to clindamycin (15.1%) but no resistance to penicillins.[73]

## Summary of evidence:

There is ample experience with both clindamycin and amoxicillin in the Netherlands. Both are cheap and are readily available. No comparative data are available regarding the efficacy of amoxicillin versus clindamycin for the treatment of PJI caused by *C. acnes*. The quality of the available evidence is therefore very low. According to the expert group, both amoxicillin and clindamycin can be used to treat *C. acnes* PJI. We advise basing the choice for a particular regimen on antibiotic susceptibility, tolerance to antibiotics and patient feasibility. Amoxicillin has a different antibacterial spectrum compared with clindamycin but is associated with more drug (gastro-intestinal) side effects and drug hypersensitivity. Clindamycin is associated with more damage to the microbiome, possibly resulting in *Clostridioides difficile* associated diarrhoea. Both antibiotics are used as treatment for other bone and joint infections and are relatively cheap. Given the increasing prevalence of antimicrobial resistance to clindamycin, and the lesser effect on (anaerobe) flora, it seems valid to prefer use of amoxicillin for *C acnes* PJI. The strength of the recommendation is conditional.

PICO 5b: In a person with a PJI caused by *Cutibacterium (Propionibacterium) acnes*, is a rifampicin-based regimen more effective in achieving clinical cure than treatment regimens without rifampicin?

## **Recommendation:**

We suggest not to treat *Cutibacterium acnes* PJI with a rifampicin-based regimen. Strength of recommendation: conditional, quality of evidence: low

## Rationale:

Treatment of PJI caused by *Cutibacterium acnes* is complicated by the formation of bacterial biofilms which shield microorganisms from the host immune system and antibiotic treatment.[74] The addition of rifampicin has been shown to improve cure rates of biofilms formed by *Cutibacterium acnes* in vitro and in an animal foreign-body infection model.[75] For these reasons, it has been speculated that a rifampicin-based regimen is more effective in treating PJI than antibiotic regimens that do not contain rifampicin.

The *Cutibacterium acnes* subset of the meta-analysis performed by Aydın et al.,[43] showed no difference in infection control between subjects with PJI treated with a rifampicin-based regimen and those treated with a non-rifampicin based regimen. Also both the individual retrospective cohort studies that were included in the meta-analysis did not show a beneficial effect of adding rifampicin. [76, 77] A more recent study in patients with PJI caused by *C. acnes, C. avidum or C. granulosum* did observe less treatment failures in the group treated with a rifampicin-based regimen.[78] However, the effect of adding rifampicin was not significant when adjusting for surgical strategy and overall duration of antibiotic treatment (adjusted HR = 0.50; 95% CI, 0.23-1.05; P-value = .07).

## Summary of evidence:

The beneficial effect of a rifampicin-based regimen for the treatment of PJI caused by *C. acnes* is not supported by the currently available studies in humans. However, conducted studies are scarce, have fairly small sample sizes and are of suboptimal design (being mostly retrospective cohort studies). Future randomised-controlled trials are needed to draw conclusions regarding the possible beneficial effect of adding rifampicin to treatment regimens for PJI caused by *C. acnes*. We lowered the quality of evidence from moderate to low given the suboptimal design of the studies. Given the low quality of evidence and the possibility of adverse effects and drug-drug-interactions with the use of rifampicin, we give a conditional recommendation not to give a rifampicin-based therapy to patients with a *C. acnes* PJI.

## Candida

PICO 6: In a person with a PJI caused by *Candida*, is initial treatment with fluconazole as effective as treatment with other antimycotic drugs?

## **Recommendation:**

We suggest to treat persons with a PJI caused by *Candida* species with fluconazole as initial regimen if the *Candida* is susceptible to fluconazole, the implant is exchanged, and the patient does not have candidemia.

If susceptibility to azole compounds is unknown we suggest to start treatment with anidulafungin.

Strength of recommendation: conditional, quality of evidence: low

#### Rationale:

PJI by *Candida* spp. is a rare complication following joint arthroplasty. There are no standard recommendations regarding the management of these infections. According to international guidelines the two stage revision surgery in combination with an antifungal agent for at least 12 weeks between operations is considered the optimal treatment with a success rate of 93%.[10, 79, 80] However, the optimal agent and duration of treatment are not well known. Treatment outcome may also largely depend on intrinsic or acquired resistance of *Candida* spp. to specific antifungal drugs and distribution of the antifungal agents in bone and synovial fluid. MIC's of fluconazole for *C. glabrata* and *C. krusei* are higher than for other *Candida* spp. and *C. parapsilosis* is known to be intrinsically less susceptible to echinocandins. Bone and synovial fluid concentrations of fluconazole and liposomal amphotericin B are high. Limited data are available for anidulafungin and no data for caspofungin or micafungin.[81] Ecchinocandins can often be clinically effective due to their immunomodulatory properties and the fact that they successfully penetrate biofilms. However, as the implant is usually removed in Candida PJI and biofilm removed this might not be relevant anymore for treatment outcome.

### Studies:

Kim et al., performed a systematic review and pooled analysis of the literature between 1950 and 2014 on the treatment and outcome of *Candida* spp. infection after total hip arthroplasty.[82] They included 20 papers with 37 patients in total. *C. albicans* (58%) and *C. glabrata* (18%) were the most commonly identified pathogens. A 2-stage exchange and antifungal therapy for a median of 6 weeks between procedures had a success rate of 93%. There was no consensus regarding the type and dose of systemic antifungal agents. Three patients had a relapse after 1-33 months, all after retention of the prosthesis. Three patients died from candidemia and sepsis despite resection and removal of the prosthesis, all after initial treatment with fluconazole. No deaths occurred in the group treated with another agent.

Koutserimpas et al.,[83] performed a review of the literature through 2018 on the treatment of non-albicans *Candida* PJI's, most often treated with 2-stage revision or excision. They included 83 patients with knee (62,6%), hip (35%) and shoulder (2,4%) joint prosthesis. *C. parapsilosis* (54,2%), *C. glabrata* (21,7%) and *C. tropicalis* (12%) were the most prevalent non-albicans *Candida* spp. Fluconazol was the preferred antifungal agent (71%), in over half of the cases given as monotherapy. Amphotericin B was given in 49% and flucytosine, caspofungin, anidulafungin, voriconazol, ketoconazole or itraconazole in 25% of patients mostly in combination with one or more other antifungal agents. The overall success rate was 89.2%.

*C. parapsilosis* PJIs were not treated with echinocandins as MICs are usually elevated. Treatment was successful in 88.9% of the studied cases. *C. glabrata* is usually resistant to azoles. For the treatment of *C. glabrata* PJIs, an azole compound was rarely used and treatment was successful in 94.4%. In most cases of other non-albicans *Candida* PJIs, treatment has been successful with either a single antifungal agent or combinations known to be effective against this *Candida* spp.

## Summary of evidence:

Even though there has been a systematic review that compared outcomes of patients treated for *Candida* PJI, we did not find RCTs or high-quality retrospective cohort studies that directly compared outcomes of azole, amphotericin B and/or echinocandin treatment for *Candida* PJI. The studies mostly studied patients treated with 2-stage revisions (without retainment of prosthesis). It seems

valid not to perform a one-stage revision or DAIR procedure in case of *Candida* PJI since there are no data to support these surgical techniques. The overall success rate of treatment is high in the identified studies for all antifungal treatments. It seems valid to prescribe echinocandins for patients with a PJI and candidemia. Both fluconazole and amphotericin B give high drug levels in joint and bone tissue. Less data are available for echinocandins. Given the paucity of evidence for a certain antifungal drug, we suggest using the easiest, cheapest (and oral) alternative, i.e., azole therapy in case of azole-sensitive *Candida* infection and the implant is exchanged. The quality of evidence is lowered from moderate to low given the high chance of bias in the studies.

## **Culture-negative**

PICO 7: In a person with a culture-negative PJI, is a fluoroquinolone combined with rifampicin regimen as effective as any other treatment in achieving clinical cure?

## **Recommendation:**

We suggest not to use a fluoroquinolone combined with rifampicin as a standard treatment for culture-negative PJI.

Strength of recommendation: conditional, quality of evidence: very low

## **Recommendation:**

We recommend to determine antimicrobial strategies for culture-negative PJI on an individual basis (e.g., taking into account prior antibiotic use, host characteristics and symptoms)

Strength of recommendation: strong, quality of evidence: very low

## Rationale:

A PJI is defined as culture-negative if it does fulfil the criteria for PJI as defined by the EBJIS [84] but cultures are negative. It is important to determine whether the culture outcome is a true-negative or false-negative due to the presence of rare or hard-to-culture microorganisms such as mycobacteria and fungi.[85] The Working Group recommends that in case of a CN PJI (for example only an elevated synovial leukocyte count or a positive  $\alpha$ -defensin test in the synovial fluid), additional efforts should be made to determine the causative agent, for example, by serology, species-specific PCR, a 16S-PCR or repeat diagnostic biopsies. Furthermore, if cultures are negative, the differential diagnosis of a non-infectious arthritis should be worked out.

Of the patients with PJI, 0-42% is culture negative. [85] This heterogeneity is probably related to the fact that not in all CN PJIs all efforts were done to find a causative micro-organism like described above. Prior antibiotic use is associated with CN PJI. [86, 87] A broad spectrum regimen covering gram-positive, gram-negative organisms and anaerobic organisms might be considered for treating culture-negative PJI. A systematic review was conducted to examine whether a fluoroquinolone combined with rifampicin regimen is as effective as treatment with other antibiotics.

We found no studies that compared different antibiotic regimens for the treatment of CN PJI. Two systematic reviews show that in most studies regarding CN PJI, subjects received either vancomycin alone or in combination with another antibiotic. [85, 88] In only one study, [89] the majority of patients received a fluoroquinolone combined with rifampicin. This study, in which all patients received levofloxacin combined with rifampicin, showed that no re-infections occurred in the 19 included subjects with CN PJI. In this study, the difference in re-infection rate between the CN and culture positive group was not statistically significant. This suggests levofloxacin combined with rifampicin might be a good treatment option for CN PJI, but the chance of bias is high due to the

small study population and the retrospective nature of this study. In a retrospective cohort study,[86] vancomycin was used only in 29.6% of the cases with CN PJI, most people received a cephalosporin (85.2%). Only 2 cases (7.4%) received ciprofloxacin in this study. This study suggests that since reasonable treatment outcomes were obtained, extensive utilisation of vancomycin in CN PJI might be unwarranted. On the contrary, another retrospective cohort study did find higher infection control rates in the CN PJI group treated with vancomycin based regimen compared with other antibiotic treatment options.[90] However, only one of the subjects who did not receive vancomycin, was treated with a fluoroquinolone (combined with daptomycin, not rifampicin). Other studies did not give insights into the differences of effectiveness of different antibiotic regimens for the treatment of CN PJI.

## Summary of evidence:

We did not identify studies that compared different regimens in CN PJI. There was one retrospective cohort study that did not suggest a difference in outcome between patients with CN PJI treated with levofloxacin and rifampicin and those with PJI treated based on culture results. We downgraded the evidence two levels because of indirectness and the small study size. Since there is insufficient evidence available to determine if a fluoroquinolone based regimen combined with rifampicin is as effective as other treatment options in achieving clinical cure for CN PJI, and the combination therapy can have side effects and drug-drug interactions, we conditionally recommend not to use the combination as a standard option for patients with CN PJI. We recommend to base the antimicrobial advice on the individual features of the infection in the particular patient (previous culture results, allergies, molecular microbiological analysis). Although we did not identify studies that support the use of additional features to direct antimicrobial therapy, we do think that this is particularly important in patients with CN PJI. Therefore, the second recommendation is strong (based on low level evidence.

## 6. Chronic suppressive antibiotic therapy

In the currently available literature, different definitions are used for suppressive therapy. In this guideline we define suppressive antibiotic therapy as the chronic use of antimicrobial therapy for an established PJI for patients who are unsuitable for, or refuse, DAIR, excision arthroplasty or amputation. Suppressive therapy is only started after treatment of the osteomyelitis around the implant for at least six weeks. Thereafter, treatment can be continued with long term oral antibiotics, usually at a lower dose. The aim of suppressive therapy is to prevent a flare-up of the infections from the chronically infected prosthesis. The decision to start chronic suppressive therapy must take into account the individual circumstances of the patient including the presence of draining fistulae (in these cases suppressive therapy is generally withheld), the availability of suitable treatment options and the potential toxicity of prolonged antibiotic therapy. Suppressive therapy can be stopped when the prosthesis is removed. Current guidelines do not offer clear recommendations regarding the duration of suppressive therapy when prosthesis remains in situ. It is unknown whether viable bacteria residing within chronic biofilms are still present after a certain period of adequate antibiotic suppressive treatment. We therefore searched the available literature on whether suppressive therapy can be safely stopped after a prolonged period of 2 years.

## PICO 8: Can suppressive antibiotic therapy in a person with a PJI be stopped after 2 years?

## **Recommendation:**

We suggest to base the decision on the duration of chronic suppressive antimicrobial therapy on an individual basis (e.g., taking into account toxicity of antibiotics and host characteristics)

Strength of recommendation: conditional, quality of evidence: very low

#### **Recommendation:**

We suggest to withhold chronic antimicrobial suppressive therapy in patients with a draining sinus tract.

Strength of recommendation: conditional, quality of evidence: very low

#### Rationale:

Systematic search yielded no studies that compared suppressive antibiotic therapy (SAT) for less than two years with SAT with more than two years for the treatment of PJI. One study found that of the patients with initial improvement after starting therapy, 55% (n=17) remained relapse free after stopping antibiotics for longer than six months.[91] However, limitations of this study are its retrospective nature, the lack of control group, heterogeneous study population and the wide ranges in duration of SAT and follow-up time. Moreover, this study does not compare outcomes between subjects who received SAT for different lengths of time. None of the other studies that were found assessed the relapse rate after stopping SAT; They only assessed the relapse rate while still using SAT.

#### Dosing of chronic suppressive antibiotic therapy

The dosing of suppressive antimicrobial treatment differs between many treatment centers. The IDSA guidelines for treatment of PJI (2013) [3] recommends to lower the dose for suppressive antimicrobial treatment. Based on these IDSA recommendations and clinical experience within the committee, we suggest to use a lower than standard dosage when starting suppressive antimicrobial treatment. The underlying rationale for using a lower dosage is that suppressive antibiotic therapy is only started after the initial treatment of the osteomyelitis for a period of at least six weeks. In those cases, suppressive treatment is aimed to prevent outgrowth of dormant bacteria within the biofilm causing a relapse of infection. In these situations, a therapeutic dose of antibiotics may not be needed. Clinical and laboratory monitoring for efficacy and safety is needed, based on the clinical judgement of the clinician who cares for the patient.

#### Summary of evidence:

We did not find literature to support administering two years of suppressive antibiotic treatment for two years. There was consensus in our group that chronic suppressive antimicrobial therapy should be withheld to patients with a draining sinus tract since it is unlikely that the patient will get severely ill from the infection. Furthermore, selection of strains with antimicrobial resistance or development of antimicrobial resistance of bacteria already existing in the joint to the suppressive antimicrobial is likely. We suggest to base the decision on the duration of chronic suppressive antimicrobial therapy on the patients' personal circumstances (e.g., toxicity of antibiotics and host characteristics) and that these should be discussed on a case-by-case basis. Suggestions on how to dose suppressive therapy are given in Table 4, based on the IDSA guideline and expert opinion.

## 7. Duration of therapy, route of administration and dosages

The duration of antimicrobial treatment for PJI is dependent on the type of surgery that is performed. The Infectious Diseases Society of America (IDSA) guidelines recommends a 6-week course of intravenous antimicrobial therapy or highly bioavailable oral antimicrobial therapy following resection arthroplasty for PJIs.[3] For patients with staphylococcal PJI treated with 1SR and DAIR, 2 to 6 weeks of pathogen-specific intravenous antimicrobial therapy in combination with rifampin followed by rifampin plus a companion oral drug for a total of 3 months is recommended. The consensus document does not give detailed advice on switching to oral therapy. [5] Furthermore, the IDSA guidelines recommend longer treatment for patients undergoing DAIR and 1SR than patients treated with 2SR (12 weeks and 6 weeks, respectively).[3] Shorter courses of antibiotics might have similar rates of success as 12-week courses. [92, 93] The doses used in the studies varied. In other guidelines, [3] high doses are recommended in the treatment of PJI because of theoretical considerations: high levels of antibiotics are needed to penetrate the glycocalyx and kill bacteria in sessile phenotypes in biofilms; In comparable infections, e.g., artificial valve endocarditis, the highest tolerable doses are recommended; [94] A PJI is a serious infection where undertreatment could have large consequences such as limb loss, loss of life and loss of quality of life. On the other hand, lower doses are currently used in most of the centres in the Netherlands; The experience of the members of group is that high, but not the highest doses of antibiotics suffice; Theoretically, lower doses would lead to fewer side effects and lower costs; Surgery is needed to cure biofilm related infections, not antibiotics alone. The surgery would lead to disruption of the biofilm, making it less necessary to treat with the highest tolerable dose; There are no outcome data to support the use of the highest possible doses.

There was no consensus in the committee on the recommended dosages and dosage intervals for some of the antibiotics. Recommended dosages are always in the high range (e.g., flucloxacillin 6 gram per 24 hours). Some committee members generally recommend higher dosages, comparable with dosages administered in other severe infections such as infective endocarditis (e.g., flucloxacillin 12 gram per 24 hours). Although there are no studies that suggest either dosage leads to better outcomes, there are theoretical advantages to using higher doses. The bacteria in PJI are usually attached to the prosthesis in a biofilm, and are therefore less susceptible to antimicrobial therapy. Most of the recommended antibiotics have a large therapeutic range, and will usually not cause more side effects in the higher dosages. Disadvantages of the highest dose are that, although not very likely, higher dosages can cause more side effects (e.g., more nephrotoxicity of flucloxacillin in higher dosages, convulsions in higher dosed beta lactam antibiotics). Furthermore, higher drug dosages are generally more expensive. We chose to recommend the high dose and not the highest dose in the table. However, the highest dose can explicitly also be recommended. The highest dose is added in the legend of the table with recommended antibiotics.

PICO 9a: In a person with an acute PJI treated with DAIR, is 6 (or 8) weeks of antibiotic therapy enough to achieve clinical cure compared with 12 weeks of antibiotic therapy?

#### **Recommendation:**

We recommend to treat patients with acute PJI who undergo DAIR for 12 weeks with antibiotics

Strength of recommendation: strong, quality of evidence: high

#### Rationale:

We found 6 articles that studied the effect of the length of antibiotic treatmenton clinical outcome in subjects with PJI treated withDAIR. Only one study reported inferior outcomes in patients treated for

6 to 8 weeks of antibiotics, compared with patients whoreceived longer courses of antibiotics. A randomised controlled trial showed similar cure rates for acute staphylococcal PJI managed with DAIR and levofloxacin and rifampicin in the group treated with 8 weeks versus those treated for 3 months (hip PJI) or 6 months (knee PJI).[95] However, in this study, patients were excluded if the treating physician considered the patient having a high risk of failure. A retrospective cohort study in patients undergoing DAIR for knee or hip PJI, found no significant difference in rates of long-term remission between those receiving 6 weeks versus those receiving 12 weeks of antibiotic therapy.[96] Another retrospective cohort study with a similar study population also found that treatment outcomes were not different for subjects who received 3 months of antibiotics in knee PJIs and 2 months of antibiotics in hip PJIs compared with those who received longer antibiotic courses.[97] In a prospective cohort study in patients with PJI who underwent DAIR (29%), 1SR, 2SR or no surgical procedure, no difference in outcomes was seen between patients receiving 6 versus those receiving 12 weeks of antibiotics.[98]

One systematic review and meta-analysis was conducted that investigated subjects with acute PJI, including subjects who underwent DAIR, and compares short courses of antibiotics with longer courses of antibiotics.[99] Notably, this review is not specific for PJI treated with DAIR but also includes subjects who underwent 1SR and 2SR. This review identified 10 articles (9 observational studies, 1 RCT). The meta analysis suggested no significant difference between short courses of antibiotics versus longer courses showed no significant difference in treatment outcomes. Remarkably, they also found that shorter antibiotic courses lead to better outcomes in older study populations.[99]

One retrospective cohort study of 39 patients with PJI demonstrated that 2 weeks of IV therapy followed by 3 months of oral therapy was sufficient to control staphylococcal infections.[100] In another study 2 weeks of IV only antibiotic therapy following incision and drainage and and 2SR implantation of an antibiotic-impregnated cement spacer, results in a 87% success rate.[101]We did not identify papers that studied if biomarkers or clinical symptoms can be used to monitor response to treatment. Observation data suggest that clinicians can identify patients that require prolongation of antibiotic treatment beyond 6 weeks.

The DATIPO study was a large randomised controlled trial that challenged the findings of observational studies just discussed. This RCT found that 6 weeks of antibiotic treatment in DAIR was inferior to 12 weeks (31% versus 15% failure rate, respectively) for various pathogens.[102] A limitation of this RCT was that patients were randomised at the start of antimicrobial treatment, while it would have been more rational to randomise them in week 6, which is the moment that clinicians normally would decide whether treatment could be stopped or prolonged for another 6 weeks. Secondary, the proportion of patients with S. aureus was higher in the 6-weeks arm (38%) compared to the 12-weeks arm (30%). The RCT contradicts the observational studies in which 6 weeks of treatment was noninferior to 12 weeks. The only other study we found that suggests that prolonged antibiotic therapy after DAIR in patients with acute PJI might be beneficial is a case-control study.[103] This study, however, is prone to bias due to its study type and small study population.

#### Summary of evidence:

Most observational studies found no difference in outcome between 6 and 12 weeks of antibiotic treatment after DAIR. Since the studies compared 6 to 12 weeks, there is no rationale to treat for longer than 12 weeks. The large DATIPO study,[102] however, showed that outcomes after 12 weeks of treatment were superior to 6 weeks of antibiotics. Although there was some inconsistency, the quality of evidence was high. We found no relevant indirectness and impreciseness. Although the recommendation is strong and we think 12 weeks of treatment is the optimal duration, 6 weeks of therapy will likely suffice in some patients. We advise that the decision on the duration of

antimicrobial therapy beyond six weeks should also take into account the patients' personal circumstances (e.g., host characteristics and the biochemical and clinical response to therapy.

PICO 9b: In a person with a chronic PJI treated with 1SR, is 4 (or 6) weeks of antibiotic therapy enough to achieve clinical cure compared with 12 weeks of antibiotic therapy?

#### **Recommendation:**

We suggest to treat patients with chronic PJI who undergo 1SR for 6 weeks, but the duration can be lengthened to 12 weeks depending on clinical circumstances. Strength of recommendation: conditional, quality of evidence: low

#### Rationale:

Literature search yielded 4 applicable studies investigating the length of antibiotic courses after 1SR for the treatment of PJI. Only one study looked solely at the effect of length of antibiotic treatment after 1SR, and did not also include patients with PJI treated with two-staged revision (2SR) or debridement, antibiotics and implant retention (DAIR).[104] This case series showed that a six weeks course of antibiotics in hip and knee PJI treated with 1SR resulted in a satisfactory remission rate of 90%. Of the 50 included patients, 41 had a PJI of a prosthesis that was in situ for more than three months. A prospective cohort study by Bernard et al. found no differences in treatment outcomes for subjects with PJI treated with 1SR, 2SR or DAIR who received antibiotics during 6 versus 12 weeks.[98] However, only 6% of these patients were treated with 1SR which makes this study less suitable for drawing conclusions regarding the length of antibiotic treatment for patients treated with 1SR. A case-control study showed the odds of recurrence of implant-related infections was higher for patients with antibiotic treatment lasting longer than 14 days than for those with shorter treatment.[105] However, this study focuses on fracture fixation devices and not PJI. Furthermore, this study does not mention how many of the subjects with PJI underwent 1SR. The literature review by Yen et al. investigated the effect of the length of antibiotics on treatment outcomes of PJI.[99] But, this review included only one study (the study from Bernard et al.[98]) that examined the effect of the total (oral and intravenous) length of antibiotic course for the treatment of patients with PJI who underwent 1SR. In a substudy of 150 subjects in the DATIPO study, there was no difference in outcome in patients undergoing 1SR treated 6 weeks and 12 weeks.[102]

#### Summary of evidence:

We did not find high-quality studies on the duration of antibiotic therapy in patients with chronic infection treated with 1SR. The available data suggest that 6 weeks of antibiotic treatment leads to comparable infection cure rates as 12 weeks of antibiotic treatment. This might be explained by the surgical procedure and the better source control that can be achieved with 1SR compared with DAIR. There was no strict definition of chronicity in the identified studies. Since the studies compared 6 to 12 weeks, there is no rationale to treat for longer than 12 weeks. The quality of evidence was decreased to low because of indirectness, impreciseness and chance of bias. We think that the decision on the duration of antimicrobial therapy should also take into account the patients' personal circumstances (e.g., toxicity of antibiotics, host characteristics and (biochemical and clinical) response to therapy). For most cases, 6 weeks of therapy will likely suffice in patients with a clear clinical improvement and normalised CRP after 6 weeks of antimicrobial treatment. The recommendation is conditional. Although most studies examined 1SR, we also think that the same duration can be used in patients undergoing 2SR.

## 8. Timing of therapy

PICO 10: In a person with a chronic PJI treated with two-stage revision surgery, is antibiotic holiday/withholding of antibiotics before reimplantation more effective in achieving clinical cure compared with no antibiotic holiday?

#### **Recommendation:**

We suggest not to delay reimplantation after finishing antibiotic treatment in 2SR. Strength of recommendation: conditional, quality of evidence: very low.

#### Rationale:

Many practitioners use an antibiotic-free period, colloquially termed 'antibiotic holiday', before reimplantation of joint prosthesis in the second stage of a two-stage exchange arthroplasty. The rationale behind this holiday is that persistent infection is likely to exhibit while the patient is off antibiotics and the changes of false negative cultures during reimplantation decreases. Clinical improvement of the patient during this period signifies infection eradication, while deterioration expressed by inclining serum markers (ESR, CRP), fever or joint pain, suggests recurrence or persistence of infection. The influence and optimal duration of an antibiotic-free period has not been studied extensively and the evidence to support the clinical utility of an antibiotic holiday remains inconclusive. The International Consensus meeting does not recommend the use of an antibiotic holiday before reimplantation as a means of ensuring eradication of infection, citing a lack of evidence in support of this practice.[5]

Two studies were included after our systematic review on this topic. In a prospective cohort study,[106] reimplantation with discontinuation of antibiotic therapy of two weeks (N=82, median 15 days) was compared with reimplantation without discontinuation of antibiotics (N=114). A higher cure rate was found in the control group without discontinuation (91% vs 79%, p=0.029), perhaps attributable to the 46 immunocompromised patients in the control group versus 31 in the intervention group (41/46 vs 20/31; X²=5.4, P=.02) The second included study by Tan et al., concludes that the antibiotic holiday period does not affect treatment success in patients who are reimplanted; however, many patients failed in the antibiotic holiday period, which suggests that the antibiotic holiday period may be useful in detecting persistent or recurrent infection.[107] In the multivariate analysis, the duration of the holiday period (1, 2, or 4 weeks) did not appear to influence the subsequent failure rate in patients who were reimplanted (OR, 0.93 per week; 95% CI, 0.81-1.06; P= .250).

#### Summary of evidence:

Available non-randomized studies to antibiotic discontinuation in 2SR suggest that there might be a better outcome in patients treated without antibiotic discontinuation. The consensus group noted that patients treated with 2SR are usually treated empirically with antibiotics at the reimplantation, the second stage of the 2SR procedure, until perioperative culture results are negative. If cultures are positive, the patient is treated with antibiotics, analogous to a 1SR. There is substantial inconsistency, impreciseness and high chance of bias in the studies. The quality of evidence was decreased to very low. Although the panel does not think that antibiotic holidays are necessary and will lead to delay, there are no strong objections to withholding antibiotic therapy before reimplantation as long as the infection has been treated adequately for six weeks and there are no signs of ongoing infection. The lack of high level evidence leads to a conditional recommendation.

PICO 11: In a person with an acute PJI caused by staphylococci and treated with DAIR, should you defer the start of rifampicin until the wound is no longer draining?

#### **Recommendation:**

We suggest not to defer the start of rifampicin until the wound stops draining in a person with an acute PJI caused by staphylococci and treated with DAIR Strength of recommendation: strong, quality of evidence: very low.

#### Rationale:

Rifampicin is a drug with a low genetic threshold for the development of antimicrobial resistance. Only a point-mutation is necessary for staphylococci to become resistant. In vitro studies demonstrate a high rate of rifampicin resistance in the presence of a high bacterial inoculum when rifampicin monotherapy is applied. In a similar fashion, rifampicin resistance could theoretically develop if inadequate drug levels of the co-antibiotic administered together with rifampicin reach the surgical site. One retrospective study demonstrated that patients who received rifampicin prior to surgical debridement and received less than 2 weeks of induction therapy with intravenous antibiotics had a higher odd of developing rifampicin resistant strains.[108] Rifampicin resistance in patients with failure after DAIR has been reported, but this was in patients who were not treated with adequate debridement, no induction treatment with IV antibiotics or with combination therapy.[108] After finishing the search strategy for this SWAB guideline, an observational study performed by Beldman et al. was published.[109] In this study, 669 patients with a PJI caused by staphylococci and treated with surgical debridement were evaluated. Starting rifampicin within 5 days after surgical debridement was an independent risk factor for failure in the multivariate analysis (aHR 1.96, 95% CI 1.08 - 3.56) but the early starters (<5d) had more Staphylococcus aureus infections (74% vs 51%), less exchange of mobile parts, and later onset of DAIR after PJI diagnosis, all of which are known to be associated with failure. Another observational study in which patients with immediate postoperative start of rifampicin were compared with later start of rifampicin, reported similar success rates.[110] To conclude, the literature supports the importance of adequate bacterial load reduction prior to the start of rifampicin and combination therapy, but does not support waiting until the wound has stopped draining.

#### Summary of evidence:

Based on the studies, rifampicin can be started after adequate surgical debridement and in combination therapy. If these conditions are met, rifampicin can be started as soon as rifampicin susceptible staphylococci are known to be the causative agents. The quality of evidence is very low (based on two observational studies).

# **Appendices**

**Appendix A: Selected PICO Questions, corresponding Search Strings and Number of Hits** 

**Appendix B: Bias Assessment** 

**Appendix C: Evidence Tables** 

# Appendix A: Selected PICO Questions, corresponding Search Strings and Number of Hits

Total number of hits 24th July 2020: 10554 5505 duplicates deleted, 5049 left for analysis

## 1. Culture directed antimicrobial therapy

#### Staphylococci

#### PICO 1a:

P Staphylococcus PJI

I rifampicin-based antibiotic regimen

C non-rifampicin-based antibiotic regimen

O cure

#### PICO 1b:

P Staphylococcus PJI

I non-fluoroquinolone combined with rifampicin

C fluoroquinolone combined with rifampicin

O cure

#### PICO 1c:

P Methicillin resistant coagulase negative Staphylococcus PJI

I Initial IV treatment with vancomycin

C Initial IV treatment with daptomycin

O cure

Search string: ("PJI"[tiab] OR (("Prostheses and Implants"[Mesh] OR "periprosthetic"[tw] OR "periprosthetic"[tw] OR "prosthetic"[tw] OR "prosthesis"[tw] OR "prostheses"[tw]) AND ("joints"[MeSH] OR "joints"[tw] OR "joints"[tw] OR "infections"[tw] OR "infections"[tw] OR "infections"[tw] OR "infections"[tw] OR "staphylococci"[tw] OR "Staphylococcus"[tw] OR "Staphyloc

#### Hits per database:

Pubmed: 1583Embase: 3185Coch/Clin: 57

#### Streptococci

#### PICO 2a:

P Streptococcal PJI

I rifampicin-based antibiotic regimen

C non-rifampicin-based antibiotic regimen

O cure

#### PICO 2b:

P Streptococcal PJI

I oral treatment with amoxicillinC oral treatment with clindamycin

O cure

Search string: ("PJI"[tiab] OR (("Prostheses and Implants"[Mesh] OR "periprosthetic"[tw] OR "periprosthetic"[tw] OR "prosthetic"[tw] OR "prostheses"[tw] OR "prostheses"[tw]) AND ("joints"[MeSH] OR "joints"[tw] OR "joints"[tw] OR "infections"[tw] OR "infections"[tw] OR "infections"[tw] OR "infectious"[tw]))) AND ("Streptococcus"[Mesh] OR "streptococcus"[tw] OR "streptococcus"[tw])

#### Hits per database:

Hits Pubmed: 284 Hits Embase: 784 Hits Coch/Clin: 5

#### Enterococci

#### PICO 3:

P: Enterococcal PJI

I Intial IV treatment with monotherapy

C Intial IV treatment with combination therapy

O: cure

Search string: ("PJI"[tiab] OR (("Prostheses and Implants"[Mesh] OR "periprosthetic"[tw] OR "periprosthetic"[tw] OR "prosthetic"[tw] OR "prostheses"[tw]) AND ("joints"[MeSH] OR "joints"[tw] OR "joints"[tw] OR "joints"[tw] OR "infections"[tw] OR "infections"[tw] OR "infections"[tw] OR "infectious"[tw]))) AND ("Enterococcus"[Mesh] OR "enterococcus"[tw] OR "enterococci"[tw] OR "enterococcal"[tw]))

#### Hits per database:

Hits Pubmed: 143 Hits Embase: 512 Hits Coch/Clin: 5

### **Gram-negative bacilli**

#### PICO 4:

P: Gram negative bacilli

I: Oral treatment with fluoroquinolone

C: Oral treatment with trimethoprim/sulfamethoxazole

O: cure

Search string: ("PJI"[tiab] OR (("Prostheses and Implants"[Mesh] OR "periprosthetic"[tw] OR "periprosthetic"[tw] OR "prosthetic"[tw] OR "prostheses"[tw]) AND ("joints"[MeSH] OR "joints"[tw] OR "joints"[tw] OR "joints"[tw] OR "infections"[tw] OR "infections"[tw] OR "infections"[tw] OR "infectious"[tw]))) AND ("Enterobacteriaceae"[Mesh] OR "Enterobacterales"[tw] OR "Gram-negative bacteria"[tw])

#### Hits per database:

Hits Pubmed: 150 Hits Embase: 682 Hits Coch/Clin: 1

#### Cutibacterium (Propionibacterium) acnes

#### PICO 5a:

P C. acnes PJI

I oral treatment with amoxicillinC oral treatment with clindamycin

O cure

#### PICO ab:

P C. acnes PJI

rifampicin-based antibiotic regimennon-rifampicin-based antibiotic regimen

O cure

Search string: ("PJI"[tiab] OR (("Prostheses and Implants"[Mesh] OR "periprosthetic"[tw] OR "periprosthetic"[tw] OR "prosthetic"[tw] OR "prostheses"[tw]) AND ("joints"[MeSH] OR "joints"[tw] OR "joints"[tw]) AND ("infections"[MeSH] OR "infection"[tw] OR "infections"[tw] OR "infectious"[tw]))) AND ("Cutibacterium"[tw] OR "Cutibacterium acnes subsp. acnes" [Supplementary Concept] OR "Propionibacterium"[tw] OR "Propionibacteriaceae"[Mesh] OR "acnes"[tw])

#### Hits per database:

Hits Pubmed: 228 Hits Embase: 468

#### Candida

#### PICO 6:

P Candida PJI

I 2 weeks intial treatment with fluconazole therapy

C 2 weeks intial treatment with other therapy

O cure

Search string: ("PJI"[tiab] OR (("Prostheses and Implants"[Mesh] OR "periprosthetic"[tw] OR "periprosthetic"[tw] OR "prosthetic"[tw] OR "prostheses"[tw]) AND ("joints"[MeSH] OR "joints"[tw] OR "joints"[tw]) AND ("infections"[MeSH] OR "infection"[tw] OR "infections"[tw] OR "infections"[tw])) AND ("Candida"[mesh] OR "Candida"[tw])

#### Hits per database:

Hits Pubmed: 121 Hits Embase: 275

#### **Culture-negative**

#### PICO 7:

P: Culture-negative PJI

1: fluoroquinolone combined with rifampicin

C: other antibiotic regimen

O: Cure

Search string: ("PJI"[tiab] OR (("Prostheses and Implants"[Mesh] OR "periprosthetic"[tw] OR "periprosthetic"[tw] OR "prosthetic"[tw] OR "prosthesis"[tw] OR "prostheses"[tw]) AND ("joints"[MeSH] OR "joints"[tw] OR "joint"[tw]) AND ("infections"[MeSH] OR "infection"[tw] OR "infections"[tw] OR "infectious"[tw]))) AND ("culture-negative"[tw] OR "negative culture"[tw])

#### Hits per database:

Hits Pubmed: 147 Hits Embase: 179 Hits Coch/Clin: 4

## 2. Suppressive therapy

#### PICO 8:

Ρ Suppressive AB for incurable PJI

ı <2y of suppressive AB

C >2y of suppressive AB

0 Need for surgical reintervention

Search string: ("PJI"[tiab] OR (("Prostheses and Implants"[Mesh] OR "periprosthetic"[tw] OR "periprosthetic"[tw] OR "prosthetic"[tw] OR "prosthesis"[tw] OR "prostheses"[tw]) AND ("joints"[MeSH] OR "joints"[tw] OR "joint"[tw]) AND ("infections"[MeSH] OR "infection"[tw] OR "infections"[tw] OR "infectious"[tw]))) AND ("suppressive treatment"[tw] OR "suppressive therapy"[tw] OR "conservative treatment"[tw] OR "conservative therapy"[tw] OR "suppression"[tw])

#### Hits per database:

Hits Pubmed: 99 Hits Embase: 337 Hits Coch/Clin: 1

## 3. Duration of therapy

#### PICO 9a:

P: Acute PJIs treated with DAIR

I: 6 or 8 weeks of antibiotic treatment C: 12 weeks of antibiotics treatment

Cure O:

#### PICO 9b:

P: Chronic PJIs treated with one-stage revision surgery

l: 4 or 6 weeks of antibiotic treatment C:

12 weeks of antibiotic treatment

O: Cure

Search string: ("PJI"[tiab] OR (("Prostheses and Implants"[Mesh] OR "periprosthetic"[tw] OR "periprosthetic"[tw] OR "prosthetic"[tw] OR "prosthesis"[tw] OR "prostheses"[tw]) AND ("joints"[MeSH] OR "joints"[tw] OR "joint"[tw]) AND ("infections"[MeSH] OR "infection"[tw] OR "infections"[tw] OR "infectious"[tw]))) AND ("Duration of Therapy"[Mesh] OR"duration of therapy"[tw] OR "duration of

treatment"[tw] OR "duration of antimicrobial"[tw] OR "duration of antibiotic"[tw] OR "therapy duration"[tw] OR "treatment duration"[tw] OR "treatment time"[tw] OR "therapy time"[tw] OR "weeks therapy"[tw] OR "months therapy"[tw])

#### Hits per database:

Hits Pubmed: 63 Hits Embase: 632

## 4. Timing of therapy

#### **PICO 10:**

P: Chronic PJI treated with two-stage revision surgery

I: Reimplantation after antibiotic holiday/withholding of antibioticC: Reimplantation without antibiotic holiday/withholding of antibiotic

O: Cure

Search string: ("PJI"[tiab] OR (("Prostheses and Implants"[Mesh] OR "periprosthetic"[tw] OR "periprosthetic"[tw] OR "prosthetic"[tw] OR "prostheses"[tw] OR "prostheses"[tw]) AND ("joints"[MeSH] OR "joints"[tw] OR "joints"[tw] OR "infections"[tw] OR "infections"[tw] OR "infections"[tw] OR "infections"[tw] OR "two-stages"[tw] OR "two-stages"[tw] OR "two stages"[tw] OR "two-stages"[tw] OR "two-stages"[tw]

#### Hits per database:

Hits Pubmed: 8 Hits Embase: 36

#### **PICO 11:**

P: Acute staphylococcal PJI treated with DAIR

I: Immediate start of rifampicin after surgical debridement

C: Delayed Start of rifampicin when the wound is dry / sensitivity is known

O: cure

Search string: ("PJI"[tiab] OR (("Prostheses and Implants"[Mesh] OR "periprosthetic"[tw] OR "periprosthetic"[tw] OR "prosthetic"[tw] OR "prostheses"[tw]) AND ("joints"[MeSH] OR "joints"[tw] OR "joints"[tw]) AND ("infections"[MeSH] OR "infection"[tw] OR "infections"[tw] OR "infectious"[tw]))) AND ("timing"[tw] OR "immediate"[tw] OR "immediately"[tw] OR "delay"[tw] OR "delay"[tw] OR "delayed"[tw] OR "start"[tw] OR "starting"[tw] OR "started"[tw] OR initiat\*[tw] OR "Time-to-Treatment"[Mesh] OR "time to treatment"[tw] OR await\*[tw] OR wait\*[tw] OR prompt[tw] OR promptly[tw] OR instantly[tw]) AND ("Staphylococcus"[Mesh] OR "staphylococci"[tw] OR "S. aureus"[tw] OR "Staphylococcus"[tw] OR "Staphylococcus"[tw] OR "Cons"[tiab])

#### Hits per database:

Hits Pubmed: 184 Hits Embase: 418

## Extra Search 24th July 2020 - 12th Jan 2021

#### Total hits 184

Staph 93

Strep 8

Enterococ 7

Enterobac 8

Cacnes 21

Candida 7

Culture Negative 12

Suppressive 10

Duration 5

Holiday 2

Timing 11

# **Appendix B: Bias Assessment**

Table 1a: Risk of bias of all observational studies for PICO 1a and PICO 1b

Reference	Study groups defined	Selection bias avoided/ excluded	Interventio n clearly defined	Outcome clearly defined	Outcome assessed blind for exposure	Withdrawa I/ drop-out acceptable (<20%)	Selective loss to follow-up excluded	Major confounde rs/ prognostic factors identified and controlled	Score
Ascione et al. 2015 [33]	+	-	+	+	+	+	+	+	7/8
Ascione et al. 2017 [34]	+	-	+	+	+	+	+	+	7/8
Becker et al. 2020 [36]	+	-	+	+	-	-	-	-	3/8
Drancourt et al. 1997 [37]	-	-	-	+	-	+	+	-	3/8
Holmberg et al. 2015 [38]	+	-	+	-	-	+	+	-	4/8
Lesens et al. 2018 [39]	+	-	+	+	-	+	+	-	5/8

Lora-Tamayo et al. 2013 [40]	-	-	+	+	-	-	-	+	3/8
Senneville et al. 2011 [35]	+	-	+	-	-	+	+	+	5/8
Tornero et al. 2016 [41]	-	-	+	+	-	+	-	-	3/8
Scheper et al. 2022 [110]	+	-	+	+	-	+	+	+	6/8

**Table 1b:** Risk of bias of the included meta-analysis for PICO 1a and 1b

Refer	rence	Aydin et al. 2021 [43]
Section	on 1: Internal validity	
1.1	The research question is clearly defined and the inclusion/exclusion criteria must be listed in the paper.	+
1.2	A comprehensive literature search is carried out.	+
1.3	At least two people should have selected studies.	+

1.4	At least two people should have extracted data.	+					
1.5	The status of publication was not used as an inclusion criterion.	+					
1.6	The excluded studies are listed.	-					
1.7	The relevant characteristics of the included studies are provided.	+					
1.8	The scientific quality of the included studies was assessed and reported.	+					
1.9	Was the scientific quality of the included studies used appropriately?	+					
1.1	Appropriate methods are used to combine the individual study findings.	+					
1.1	The likelihood of publication bias was assessed appropriately.	+					
1.1	Conflicts of interest are declared.	+					
Section	Section 2: Overall assessment of the study						

2.1	What is your overall assessment of the methodological quality of this review?	+
2.2	Are the results of this study directly applicable to the patient group targeted by this guideline?	+/-
2.3	<b>Notes</b> : Only a subanalysis (regarding <i>Cutibacterium acnes</i> ) is applicable to this PICO-questi	ion.

Item	Karlsen et al. 2020 [32]
1. Were patients randomly assigned to intervention or control treatment?	+
2. Was assignment generated by an independent person or computer not determining eligibility of the patients?	+
3. Were patient or care provider blinded to the intervention?	-
4. Was the outcome assessor blinded to the intervention?	-
5. Were the patient groups similar at baseline regarding the most important prognostic indicators? (e.g. age, comorbidities, infecting microorganisms)	+
6. Were follow-up outcomes available from an adequate proportion of patients?	+

7. Were all randomized patients reported/analyzed irrespective drop-out or non-compliance (e.g. was an intention-to-treat analysis performed)	+
8. Except for the intervention, were patients groups treated equally?	+
9. Has selective reporting of outcomes been sufficiently ruled out?	+
10. Has unwanted influence of a sponsor been sufficiently ruled out?	+

PICO 1c: no studies were included

**Table 2a:** Risk of bias of included cohort studies for PICO 2

Reference	Study groups defined	Selection bias avoided/ excluded	Interventio n clearly defined	Outcome clearly defined	Outcome assessed blind for exposure	l/ drop-out	Selective loss to follow-up excluded	Major confounde rs/ prognostic factors identified and controlled	Score
Lora-Tamayo et al. 2017 [55]	+	+	+	+	-	?	?	+	5/8
Fiaux et al. 2016 [53]	+	-	+	+	=	?	?	-	3/8

Mahieux et al. 2019 [52]	+	-	+	+	-	?	?	-	3/8
Wouthuyzen- Bakker et al. 2019 [54]	+	-	+	+	-	+	+	-	5/8

## **Table 2b:** Risk of bias of included meta-analysis for PICO 2

Refer	ence	Aydin et al. 2021 [43]
Section	on 1: Internal validity	
1.1	The research question is clearly defined and the inclusion/exclusion criteria must be listed in the paper.	+
1.2	A comprehensive literature search is carried out.	+
1.3	At least two people should have selected studies.	+
1.4	At least two people should have extracted data.	+
1.5	The status of publication was not used as an inclusion criterion.	+

1.6	The excluded studies are listed.	-						
1.7	The relevant characteristics of the included studies are provided.	+						
1.8	The scientific quality of the included studies was assessed and reported.	+						
1.9	Was the scientific quality of the included studies used appropriately?	+						
1.1	Appropriate methods are used to combine the individual study findings.	+						
1.1 1	The likelihood of publication bias was assessed appropriately.	+						
1.1 2	Conflicts of interest are declared.	+						
Section	Section 2: Overall assessment of the study							
2.1	What is your overall assessment of the methodological quality of this review?	+						
2.2	Are the results of this study directly applicable to the patient group targeted by this guideline?	+/-						

2.3 **Notes**: Only a subanalysis (regarding *Cutibacterium acnes*) is applicable to this PICO-question.

Table 3: Risk of bias of included publications for PICO 3

Reference	Study groups defined	Selection bias avoided/ excluded	Interventio n clearly defined	Outcome clearly defined	Outcome assessed blind for exposure	Withdrawa I/ drop-out acceptable (<20%)	Selective loss to follow-up excluded	Major confounde rs/ prognostic factors identified and controlled	Score
Tornero et al. 2014 [58]	+	+	-	+	?	+	+	+	6/8
Kheir et al. 2017 [57]	+	+	-	+	?	+	+	-	5/8
Thompson et al. 2019 [61]	+	-	+	+	?	+	+	+	6/8
Renz et al. 2019 [59]	+	+	-	+	?	+	+	-	5/8
El Helou et al. 2008 [60]	+	-	+	+	?	?	+	-	4/8

Table 4: Risk of bias of included publications for PICO 4

Reference	Study groups defined	Selection bias avoided/ excluded	Interventio n clearly defined	Outcome clearly defined	Outcome assessed blind for exposure	Withdrawa I/ drop-out acceptable (<20%)	Selective loss to follow-up excluded	Major confounde rs/ prognostic factors identified and controlled	Score
Rodríguez- Pardo et al. 2014 [68]	+	+	-	+	?	+	+	+	6/8
Martínez- Pastor et al. 2009 [69]	+	?	-	-	?	+	+	-	3/8
Grossi et al. 2016 [72]	+	-	+	+	?	+	+	?	5/8

PICO 5a: no studies were included

Table 5a: Risk of bias of included observational studies for PICO 5b

Reference	Study groups defined	Selection bias avoided/ excluded	Interventio n clearly defined	Outcome clearly defined	Outcome assessed blind for exposure	Withdrawa I/ drop-out acceptable (<20%)	Selective loss to follow-up excluded	Major confounde rs/ prognostic factors identified and controlled	Score
Piggott et al. 2015 [77]	+	-	+	+	-	+	-	-	4/8

Jacobs et al. 2015 [76]	+	-	+	+	-	+	+	-	5/8
Kusejko et al. 2021 [78]	+	-	+	+	-	+	+	-	5/8

**Table 5b:** Risk of bias of the included meta-analysis for PICO 5b

Refer	rence	Aydin et al. 2021 [43]
Section	on 1: Internal validity	
1.1	The research question is clearly defined and the inclusion/exclusion criteria must be listed in the paper.	+
1.2	A comprehensive literature search is carried out.	+
1.3	At least two people should have selected studies.	+
1.4	At least two people should have extracted data.	+
1.5	The status of publication was not used as an inclusion criterion.	+

1.6	The excluded studies are listed.	-
1.7	The relevant characteristics of the included studies are provided.	+
1.8	The scientific quality of the included studies was assessed and reported.	+
1.9	Was the scientific quality of the included studies used appropriately?	+
1.1	Appropriate methods are used to combine the individual study findings.	+
1.1	The likelihood of publication bias was assessed appropriately.	+
1.1	Conflicts of interest are declared.	+
Section	on 2: Overall assessment of the study	
2.1	What is your overall assessment of the methodological quality of this review?	+
2.2	Are the results of this study directly applicable to the patient group targeted by this guideline?	+/-

**Notes**: Only a subanalysis (regarding *Cutibacterium acnes*) is applicable to this PICO-question.

Table 6: Risk of bias of included publications for PICO 6

2.3

Reference	Study groups defined	Selection bias avoided/ excluded	Interventio n clearly defined	Outcome clearly defined	Outcome assessed blind for exposure	Withdrawa I/ drop-out acceptable (<20%)	Selective loss to follow-up excluded	Major confounde rs/ prognostic factors identified and controlled	Score
Kim et al. 2015 [82]	+	-	+	+	-	+	-	-	4/8
Koutserimpas et al. 2019 [83]	+	-	+	+	-	+	+	-	5/8

**Table 7a:** Risk of bias of included observational studies for PICO 7

Reference	Study groups defined	Selection bias avoided/ excluded	Interventi on clearly defined	Outcome clearly defined	Outcome assessed blind for exposure	Withdraw al/ drop-out acceptable (<20%)	Selective loss to follow-up excluded	Major confounde rs/ prognostic factors identified and controlled	Score
Tirumala et al. 2020 [111]	+	-	+	-	-	+	+	-	4/8

Choi et al. 2012 [112]	+	-	+	+	-	+	-	-	4/8
Huang et al. 2012 [90]	+	-	+	+	-	+	-	-	4/8
Ibrahim et al. 2018 [87]	+	+	+	+	-	+	-	-	5/8
Wang et al. 2018 [89]	+	-	+	-	-	+	-	+	3/8
Santoso et al. 2018 [86]	+	-	+	-	-	+	-	-	3/8

**Table 7b:** Risk of bias of included systematic reviews for PICO 7

Refere	ence	Yoon et al. 2017 [85]	Reisener & Perka 2018 [88]
Sectio	n 1: Internal validity		
1.1	The research question is clearly defined and the inclusion/exclusion criteria must be listed in the paper.	+	+

1.2	A comprehensive literature search is carried out.	+	+
1.3	At least two people should have selected studies.	+	+
1.4	At least two people should have extracted data.	+	-
1.5	The status of publication was not used as an inclusion criterion.	-	-
1.6	The excluded studies are listed.	-	-
1.7	The relevant characteristics of the included studies are provided.	+	+
1.8	The scientific quality of the included studies was assessed and reported.	-	+/-
1.9	Was the scientific quality of the included studies used appropriately?	-	+/-
1.10	Appropriate methods are used to combine the individual study findings.	-	+
1.11	The likelihood of publication bias was assessed appropriately.	-	+

1.12	Conflicts of interest are declared.	+	+						
Sectio	Section 2: Overall assessment of the study								
2.1	What is your overall assessment of the methodological quality of this review?	-	+/-						
2.2	Are the results of this study directly applicable to the patient group targeted by this guideline?	-	-						
2.3	<b>Notes</b> : Reviews do not assess PICO-question directly.								

Table 8a: Risk of bias of included observational studies for PICO 8

Reference	Study groups defined	Selection bias avoided/ excluded	Interventio n clearly defined	Outcome clearly defined	Outcome assessed blind for exposure	Withdrawa I/ drop-out acceptable (<20%)	loss to follow-up	Major confounde rs/ prognostic factors identified and controlled	Score
Escudero- Sanches et al. 2020 [113]	+	-	+/-	+	-	+	-	+	
Leijtens et al. 2019 [114]									

Pavoni et al. 2004 [91]	
Prendki et al. 2017 [115]	
Pradier et al. 2018 [116]	
Prendki et al. 2014 [117]	
Rao et al. 2003 [118]	
Sandiford et al. 2020 [119]	
Wouthuyzen- Bakker et al. 2017 [120]	

## Table 8b: Risk of bias of the included meta-analysis for PICO 8

Reference	Malahias et al. 2020 [121]
Section 1: Internal validity	

1.1	The research question is clearly defined and the inclusion/exclusion criteria must be listed in the paper.	+
1.2	A comprehensive literature search is carried out.	+
1.3	At least two people should have selected studies.	+
1.4	At least two people should have extracted data.	?
1.5	The status of publication was not used as an inclusion criterion.	?
1.6	The excluded studies are listed.	-
1.7	The relevant characteristics of the included studies are provided.	+
1.8	The scientific quality of the included studies was assessed and reported.	+
1.9	Was the scientific quality of the included studies used appropriately?	+
1.1 0	Appropriate methods are used to combine the individual study findings.	+/-

1.1	The likelihood of publication bias was assessed appropriately.	-
1.1	Conflicts of interest are declared.	+
2.1	What is your overall assessment of the methodological quality of this review?	+/-
2.1	What is your overall assessment of the methodological quality of this review?  Are the results of this study directly applicable to the patient group targeted by this guideline?	+/-

Table 9a: Risk of bias of included observational studies for PICO 9a and 9b

	Study groups defined	Selection bias avoided/ excluded	Interventi on clearly defined	Outcome clearly defined	Outcome assessed blind for exposure	Withdraw al/ drop-out acceptable (<20%)	Selective loss to follow-up excluded	Major confounde rs/ prognostic factors identified and controlled	Score
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Puhto et al. 2011 [97]	+	-	+	+	-	+	-	-	4/8
Ma et al. 2020 [122]	+	-	+	+	-	?	-	-	3/8
Hsieh et al. 2009 [71]	+	-	+	+	-	+	-	-	4/8
El Helou et al. 2011 [123]	+	-	+	+	-	?	-	+	4/8
Chaussade et al. 2017 [96]	+	-	+	+	-	+	-	+	5/8
Bernard et al. 2010 [98]	+	+	+	+	-	?	-	+	5/8
Spitzmuller et al. 2019 [105]									

**Table 9b:** Risk of bias of included meta-analysis for PICO 9a and 9b

Refer	rence	Yen et al. 2019 [99]
Section	on 1: Internal validity	
1.1	The research question is clearly defined and the inclusion/exclusion criteria must be listed in the paper.	+
1.2	A comprehensive literature search is carried out.	+

1.3	At least two people should have selected studies.	+
1.4	At least two people should have extracted data.	?
1.5	The status of publication was not used as an inclusion criterion.	+
1.6	The excluded studies are listed.	-
1.7	The relevant characteristics of the included studies are provided.	+
1.8	The scientific quality of the included studies was assessed and reported.	+
1.9	Was the scientific quality of the included studies used appropriately?	+
1.1	Appropriate methods are used to combine the individual study findings.	+
1.1	The likelihood of publication bias was assessed appropriately.	+
1.1 2	Conflicts of interest are declared.	+

Section	Section 2: Overall assessment of the study					
2.1	What is your overall assessment of the methodological quality of this review?	+				
2.2	Are the results of this study directly applicable to the patient group targeted by this guideline?	+				
2.3	Notes:					

Table 3: Risk of bias of included randomized controlled trials for PICO 9a and 9b

Item	Benkabouche et al. 2019 [124]	Lora-Tamayo et al. 2016 [95]	Bernard et al. 2021 [102]
Were patients randomly assigned to intervention or control treatment?	+	+	+
2. Was assignment generated by an independent person or computer not determining eligibility of the patients?	+	?	+
3. Were patient or care provider blinded to the intervention?	-	-	-
4. Was the outcome assessor blinded to the intervention?	-	-	-
5. Were the patient groups similar at baseline regarding the most important prognostic indicators? (e.g. age, comorbidities, infecting microorganisms)	+	-	+

6. Were follow-up outcomes available from an adequate proportion of patients?	+	-	+
7. Were all randomized patients reported/analyzed irrespective drop-out or non-compliance (e.g. was an intention-to-treat analysis performed)	+	+	+
8. Except for the intervention, were patients groups treated equally?	+	+	+
9. Has selective reporting of outcomes been sufficiently ruled out?	+	+	+
10. Has unwanted influence of a sponsor been sufficiently ruled out?	+	+	+

# **Appendix C: Evidence Tables**

Table 1a: Evidence Table for PICO 1a, PICO 1b and 11 (Staphylococci)

Reference	Study design, setting and follow up	Study population characteristics	Intervention and control conditions	Outcome category	Results on primary and secondary outcomes + statistics	SIGN quality of evidence & Risk of Bias	Comments
Ascione et al. 2015 [33]	Prospective cohort study  Setting: Inpatient  Mean follow up in weeks: 60	Subjects (n): l: n=47 C: n=30  Mean age in years: 64 (48-82)  Male sex: 52%  Lost to follow up: n=0  Type of surgery: DAIR/2SR/SAT/ hip/knee	I: Finished rifampicin course  C: No rifampicin or unfinished rifampicin course	disappearance of all clinical and radiologic evidence of PJI coupled with CRP normalization during at least a 48-week follow-up period after the antibiotic treatment discontinuation	Outcome 1: (SA+CNS, all treatments I: 43 (cure rate 91%) C: 17 (cure rate 57%) X² = 10.9, RR 1.6, 95% CI 1.17-2.23; p = 0.0001).	SIGN quality of evidence: 2- Risk of bias: 7/8	77 Staphylococci (45 SA 32 CNS) (success rifa 43/47 vs no rifa/or intolerance 17/ 30; X² = 10.9, RR 1.6, 95% CI 1.17-2.23; p = 0.0001). (S aureus/CNS not specified)  75 pts 2 stage success (for all pathogens) rifa+36/38 (95%) vs rifa-28/37 (76%). RR 1.3 CI 1.02-1.52 p = 0.02

Ascione et al. 2017	Prospective cohort	Subjects: I: n=44	I: Rifampicin	disappearance of all clinical and	Outcome 1: (SA+CNS) I: 41 (cure rate 93%)	SIGN quality of	85 staph, (44 SA, 41 CNS), rifa + 41/44 (93%
[34]	Setting: Inpatient	C: n=41	C: No rifampicin	radiologic evidence of PJI	C: 39 (cure rate 95%) OR 0.7 (0.11-4.42) .99	evidence: 2-	success), rifa - 39/41 (95% success) (S
		Mean age in years for		coupled with CRP			aureus/CNS not
	Follow up:	all 121 cases:		normalization		Risk of bias:	specified)
	Mean 108 weeks	69 (36-80)		during a 96-week follow-up period		7/8	
		Male sex: 48%		after the discontinuation of			
		Lost to follow up (n):		antibiotic			
		I: 0		treatment			
		C:					
		Type of surgery:					
		2SR					
		Type of joint:					
		Hip					
		Knee					

Aydın et al.	Study design:	Subjects (n): total 568, 360 SA,	I: Rifampicin	remission	Outcome 1: (SA+CNS)	SIGN	8 observational studies
2021 [43]	Meta-analysis	196 CNS			I: 256 (cure rate 79%)	quality of	on SA (4 good, 2 fair, 2
	6	l:	C: No rifampicin		C: 148 (cure rate 70%)	evidence:	poor quality)
	Setting: Inpatient	n=68+22+69+44+23+31+38+60 = 325			58+14+56+41+4+21+24+41	1-	568 (360 SA, 196 CNS) Senneville SA 58/68 rifa
	inpatient	- 525 C:			= 256	Risk of bias:	succ, 19/30 no rifa succ.
		n=30+17+12+41+16+56+14+27			19+14+8+39+5+35+9+19 =	13/14	Morata: remisson SA 8/9
		= 211			148	15/11	89% (6 rifa, remission %
							n.r.), remission CNS
		Type of surgery: DAIR hip knee			Staphylococci: both fixed-		19/33 56% (18 rifa,
		(Senneville also			effects and random-effects		remission% n.r.) Aydin:
		1SR/2SR/resection/			model (REM) pooled		all pathogens combined:
		arthrodesis.			estimates were		remission 64% 14/22
		Ascione: not DAIR, only 2-stage			insignificant (OR, 1.18; 95%		rifa+, 82%14/17 rifa-).
					Cls, $[0.76; 1.82]$ ; $I^2 = 23\%$ ).		Holmberg: S aureus and
					Bayesian random-effects models produced a		CNS combined, failures in rifa – group before start
					posterior probability		rifa left out (success 66%
					density indicating that		instead of 47% for rifa-
					future studies will not		group S aureus +CNS
					favour rifampicin in		Ascione 2017: 85 staph,
					Staphylococcus infections		(44 SA, 41 CNS), rifa +
					(μ, 0.074; τ, 0.570; 89%		41/44 (93% success), rifa
					HPD, [-		- 39/41 (95% success) (S
					0.48; 0.54]).		aureus/CNS not
							specified)
							Soriano rifa+ 4/23 rifa-
							5/16
							El Helou rifa+ 21/31, rifa- 35/56
							Puhto rifa+ 24/38, rifa-
							9/14
							Chaussade rifa+ 41/60,
							rifa- 19/27

I: n.r. failure p=0.00 C: n.r. ratio univaria 0.19[0.07, 0.5 Lost to follow up (n):	use 41x ccess, 17x ire p=0.64, io univariate .06, 0.45] nultivariate 00, Inf ] IS) + olone 31 ccess, 5 (20%) .004 Hazard iriate Cox 0.53] p=0.002, te Cox 3.83] p=0.338 if rifampicin ard ratio te Cox

Drancourt et al. 1997 [37]	Study design Prospective cohort  Setting: Inpatient  Follow up: 23.5 (12-36) months after 6-9 months treatment	subjects (n): (SA+CNS) I: n=20 C: n=22  Mean age (years): I: 53.2 +/- 9.5 C: 53.1+/-20.3  Male sex: I: 65% C: 77%  Lost to follow up (n): I: 3 C: 1  Type of surgery: prosthesis 1-/2-stage revision, ostheosynthetis implant removal	I: Rifampicin and fusidic acid  C: Rifampicin and ofloxacin  THA: 6 month (and if loose 1-stage revision @5 months)  TKA: 9 months (and 1- or 2-stage @ 6 months)  Osteosynthesis: 9 months (removal @ 6 months)	remission	Outcome 1: (SA+CNS) I: 11 (cure rate 55 %) C: 11 (cure rate 50%)) P= >0.05 (N.S.)	SIGN quality of evidence: 2- Risk of bias:3/8	rifampicin+fusidic acid 23 subjects (16 prothesis), 12 SA, 11 CNS, 3 LTFU, 11/20 cured rifampicin+ofloxacin 23 subjects (13 prosthesis), 16 SA, 7 CNS, 1 LTFU, 11/21 cured  Very long treatment Missing specifying data regarding success in specific THA/TKA/SA groups
		Temoval					

Holmberg et al. 2015 [38]	Prospective case series (register) analysed Retrospectively  Setting: Inpatient  Follow up: Regarding re-revisions: Mean 4.5 yrs (2.1-??)\ Regarding other: clinical FU: >1 yr, expect 9 died <1 year, 3 missing.	subjects (n):53 SA 33 CNS (86 together:) I: n=69 C: n=17  Mean age (years): (All 145 subjects/pathogens: 70 (45–91)) I: n.r. C: n.r.  Male sex: (all pathogens: 83 (57%)) I: n.r. C: n.r  Lost to follow up (n): I: n.r. C: n.r  Type of surgery: DAIR knee (PJI based on +culture or purulence)	I: Rifampicin C: No rifampicin	Healed infection (no reoperation for PJI other than re-debridement, not died during AB, no chronic PJI or suppr AB), versus failure.	Outcome 1: (SA+CNS) I: 56 (cure rate 81%) C: 8 (cure rate 47%)) P=0.01	SIGN quality of evidence: 2- Risk of bias: 4/8	success after DAIR: for SA 38/53 (72%) (all MSSA), for CNS 26/33 (79%) (25 MRSE, 4 MSSE, 4 no info resistance). 21/30 (70%) polymicrobial (incl 9 S aureus, 17 CNS (10 MRSE, 5 MSSE; 2 no info resistance). Success after DAIR 56/69 (81%) rifamp with monomicrob staph (S aureus /CNS not specified ) PJI ++vs 8/17 (47%) without rifa.

Karlsen et al. 2020 [32]	multicentre randomized controlled trial  Setting: Inpatient  Follow up: 27 (18-99) months	subjects (n): I: n=18 rifa C: n=20  Mean age (years): All 48 pts/pathogens: 68.5 (37-92) I (all pathogens): 70 (37-92) C (all pathogens): 66 (39-84)  Male sex: I (all pathogens): 65% C (all pathogens): 68%  Lost to follow up (n): I: 0 C: 0  Type of surgery: DAIR. Hip/knee	I: Rifa combination to standard treatment  C: standard treatment: cloxacillin or vancomycin, and gentamicin sponges	In remission vs failure	Outcome 1: I: 14 (cure rate 78%) C: 13 (cure rate 65%) P=0.49	SIGN quality of evidence: 2++ Risk of bias: 8/10	Cure rate for all (38 SA, 10 CNS) rifa 17/23 (74%), non-rifa 18/25 (72%), relative risk 1.03, 95% confidence interval 0.73 to 1.45, p = 0.88). S aureus: cure 14/18 in the rifampicin group and 13/20 in the monotherapy group (95% CI 0.80–1,80; p = 0.49) Underpowered (powered for 200 subjects)

Lesens et al. 2018 [39]	Retrospective cohort,	subjects (n): I: n=89 rifa (63 rifa +FQ)	I: Rifampicin	In remission vs failure (incl	Outcome 1: I: n.s.	SIGN guality of	137 SA PJI (77 THA 57 TKA). 33 (24%) failure
. ,		C: n=48 no rifa (26 rifa -FQ)	C: No rifampicin	revision for all reasons)	C: n.s. Without rifa: unadj HR 4.3	evidence: 2-	[including chronic suppression: 47 (34%)].
		Mean age (years):			[2.07-8.94] p=0.000.		Incomplete rifa (<3
	Setting:	All 137 subjects: 73 ± 13 years;			Rifa+FQ versus other:	Risk of bias:	weeks, n=19) unadjHR
	Inpatient	l: n.r.			unadjHR 0.22 [0.09-0.55]	5/8	0.5 [0.2-1.28] 0.151.
		C: n.r.			p=0.001		Complete rifa (n=70):
	Follow up:				Rifa+FQ versus Rifa-FQ:		unadjHR 0.08 [0.018–
	24 months	Male sex:			unadjHR 0.42 [0.13-1.37]		0.36] 0.001. ROC curve:
		(All subjects 56%)			p=0.15 versus rifa without		empirical optimal cut-
		l: n.r.			FQ (n=26).		point for duration of
		C: n.r.					rifampicin: 10,5 weeks.
		Lost to follow up (n):					
		I: 0					
		C: 0					
		Type of surgery: DAIR. Hip/knee					
		тиру киес					

Lora- Tamayo et al. 2013 [40]	Study design retrospective, multicentre, observational study  Setting: Inpatient  Follow up: Not specified (>28 months)	subjects (n):total 345 l: n=303 rifa C: n=42 (?)  Mean age (years): All subjects 73 (27-95) l: n.r. C: n.r.  Male sex: All subjects: 41% l: n.r. C: n.r.  Lost to follow up (n): Total 17 (5%) (volgens Kaplan Meier 174 (54%)? l: n.r. C: n.r.  Type of surgery: DAIR. Hip/knee/other	I: Rifampicin C: No rifampicin	In remission vs failure	Outcome 1: I: n.r. C: n.r  Rifa (under therapy, after 30 days) unadjust HR 0.56 (0.31–1.01) p= 0.062, adjust HR 0.49 (0.26–0.91) p=0.024.  After therapy: unadjust HR 0.60 (.34–1.07) p=.095 rifa+levo (under therapy, after 30 days) unadjust HR 0.33 (0.12–0.92) p=0.014 (geen adjust HR) After therapy: unadjust HR 1.00 (0.56–1.77) NS	SIGN quality of evidence: 2- Risk of bias: 3/8	No specific numbers on I/C, only HR

Senneville et al. 2011 [35]	Study design Retrospective cohort  Setting: Inpatient  Follow up: 43.6 +/- 32.1 months	subjects (n): I: n=68 rifa C: n=30  Mean age (years): I: +/- 67.8 C: +/- 63.2  Male sex:	I: Rifampicin C: No rifampicin	In remission vs failure	Outcome 1: I: 58 (cure rate 75%) C: 19 (cure rate 63%) P=0.002	SIGN quality of evidence: 2+ Risk of bias: 5/8	SA PJI
		I: n.r. C: n.r.  Lost to follow up (n): I: 0 C: 0					
		Type of surgery: DAIR/1-2 stage/resection/arthrodesis. Hip/knee					

Tornero et al. 2016 [41]	Study design Retrospective analysis on prospective cohort  Setting: Inpatient  Follow up: n.r. (min >2 years after +/- 11 wks treatment)	subjects (n): total Gram pos 89 of which 53 S aureus I: n=78 rifa C: n=11  Mean age (years): All subjects: 71.9 (+/- 10.1) years I: n.r. C: n.r  Male sex: All subjects: 47% I: n.r. C: n.r.  Lost to follow up (n): I: 0 C: 0  Type of surgery: DAIR/1-2 stage/resection/arthrodesis. Hip/knee	I: Rifampicin C: No rifampicin	In remission vs failure or relapse	Outcome 1: No failure (all pathogens) 1: 68 (cure rate 87 %) C: 11 (cure rate 100%)  No relapse 1: 74 (no relapse rate 95%) C: 11 (no relapse rate 100%)	SIGN quality of evidence: 2- Risk of bias: 3/8	143 DAIR (1999 to 2013), 68 (47,6%) CNS, 53 (37.1%) SA, 55 (38,5%) poly-microbial. 92 Gram+, 21 Gram-, 30 polymicr Gram+ and Gram In Gram+ infections, rifampicin+linezolid, trimethoprim-sulfamethoxazole or clindamycin higher failure rate (27.8%, P = 0.026) than rifampicin+levofloxacin, ciprofloxacin or amoxicillin (8.3%) or monotherapy linezolid/trimethoprim-sulfamethoxazole (0%).  -Not specified for S aureus -Data do not exactly match -Many exclusions: 46 required an additional surgery to control the infection, 3 required suppressive antibiotic treatment and 4 resulted in subject death before the antibiotic treatment
							was finished.

Scheper et al. 2022 [110]	Study design: prospective registry- based cohort study  Setting: multicenter  Follow-up: minimum 1 year	Subjects: n=200  Type of PJI n=131 (66%) hip n=63 (32%) knee n=5 (2.5%) shoulder n=5 (0.5%) elbow  Type of surgery: n=189 (94%) DAIR n=11 (6%) 1SR  Mean age in years (SD): 70.3 (0.9)  Male sex: n=95 (48%)	I: short-term rifampicin groups (clindamycin or flucloxacillin or vancomycin monotherapy, including rifampicin for only 5 postoperative days)  C: long-term rifampicin group (rifampicin use for >14 days, and rifampicin use for >50% of time)	Cure - defined as absence of clinical symptoms of infection and a retained implant during at least 12 months follow up after antibiotic therapy was terminated AND if failure criteria were not met.  Failure - defined as either (1) chronic suppressive antibiotic therapy with implant retention, (2) a second debridement after finishing antibiotic therapy, (3) the need for more than 2 debridements, (4) removal of the implant, or (5) PJI-related death.	Short-term rifampicin and either flucloxacillin or clindamycin treatment (long-term rifampin based treatment as reference): adjusted hazard ratio (95% CI) = 1.21 (0.34–4.40)	SIGN quality of evidence: 2+ Risk of bias: 6/8	A short-term rifampicin strategy with either clindamycin or flucloxacillin and only 5 days of rifampicin was found to be as effective as traditional long-term rifampicin combination therapy.
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## PICO 1c: no studies were included

Table 2a: Evidence Table for PICO 2a (Streptococci)

Reference	Study design, setting and follow up	Study population characteristics	Intervention and control conditions	Outcome category	Results on primary and secondary outcomes + statistics	SIGN quality of evidence & Risk of Bias	Comments

Fiaux et al. 2016	Cohort study	Subjects: n=95	I: Rifampicin	Remission - defined as	Remission (regardless of	SIGN quality of	Rifampicin combined with:
[53]	Conort study	1: n=52	i. Kilallipicili	the absence of local or	surgical treatment):	evidence: 2-	Levofloxacin n=28 (p 0.04)
[55]		C: n=43	C: No rifampicin	systemic signs of	l: n=44	cvidence. 2	Amoxicillin n=12
		C. 11 13	e. No mampiem	implant-related	C: n=23	Risk of bias: 3/8	Trimethoprim-
	Setting: inpatient	Mean age in years: 69		infection at the last	P=0.001		sulfamethoxazole n=5
	, , , , , , , , , , , , , , , , , , ,	7		contact and the absence			Linezolid n=3
	Follow up:	Male sex:		of any new surgery or	Remission (subjects who		Teicoplanin n=2
	>2 years	I: not stated		antibiotic therapy	underwent DAIR):		Clindamycin n=1
		C: not stated		related to the	I:n=23/30		Doxycycline n=1
				streptococcal PJI	C: n=9/25		
		Lost to follow up:		assessed at least two	P=0.003		Dosage rifampicin:
		n=not stated		years after the end of			1200mg/day
				antibiotic treatment	Remission (subjects who		
		Type of surgery			underwent 1SR):		No SAT was given.
		l:			I: n=7/8		
		DAIR n=30			C: n=3/5		
		1SR n=8			P=0.25		
		2SR n=10					
		AR n=4			Logistic regression to		
		C:			identify independent		
		DAIR n=26			variables associated with		
		1SE n=5 2SE n=9			failure: DAIR, rifa-based combinations.		
		AR n=4			combinations.		
		AN 11-4			Side effects in subjects		
		Type of joint:			using combination of		
		Hip n=50			rifampicin/levofloxacin:		
		Knee n=45			33%		
		Mice ii 15			33/3		

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Aydın et al. 2021 [43]	Systematic review and	subjects (n): 483 I: n=191	I: Rifampicin	Failure: death or relapse or recurrence of PJI	Outcome failure: I:32	SIGN quality of evidence: 2+	This sys review includes 3 streptococcal PJI studies
	Meta-analysis	C: n=292	C: No rifampicin		C: 76 RR 1.78 (1.15-2.76)	Risk of bias:	(Fiaux, Mahieu, Lora- Tamayo)
	Setting:	Mean age (years) I: not stated			( ,	13/14	
	Follow up: not stated	C: not stated					
		Male sex:					
		I: not stated C: not stated					
		Lost to F/U: not stated					
		Type of surgery: DAIR					

al. Co 2017 [55] Se	Retrospective Cohort study Setting: Follow up:>2years	Failure after end of ab: n= 318 I: n=108 C: n=210  Mean age (years) I: not stated C: not stated  Male sex: I: not stated C: not stated C: not stated  Lost to F/U: not stated  Type of surgery: DAIR	I: Rifampicin C: No rifampicin	Failure = death related to infection, relapse/persistence of infection, or the need for salvage therapy.	Outcome: failure after end of AB I: 16 C: 45 RR 1.47 (0.81-2.68)	SIGN quality of evidence: 2+ Risk of bias: 5/8

Mahieux et al. 2019 [52]	Cohort study	subjects (n): 70 I: n=31	I: Rifampicin	Failure: A new sample from which the same	Outcome: failure I: 8	SIGN quality of evidence: 2-	No evaluation of survivor or selection bias.
	Setting: inpatient	C: n=39	C: No rifampicin	Streptococcus spp was isolated as was	C: 11 RR 1.08 (0.41 – 2.89)	Risk of bias: 3/8	(3x quitting rifampicin needed:1x hepatitis, 1x
	Follow	Mean age (years):77		identified in the			thrombocytopenia, 1x
	up:>2years	(69-83)		previous infected joint			severe diarrhoea)
		I: not stated		prosthesis was defined			
		C: not stated		as relapse of the infection. Isolation of			
		Male sex:38 (54%)		another microorganism			
		I: not stated		was considered as			
		C: not stated		reinfection.			
		Lost to follow up (n):					
		not stated					
		Type of surgery:					

Wouthuyzen- Bakker et al.	Cohort study	Subjects (n):95 I: 22	I: Rifampicin	Outcome: failure I:5/22 (23%)	SIGN quality of evidence: 2-	All late acute PJI
2019 [54]		C:73	C: No rifampicin	C: 31/73 (42%)		
	Setting: inpatient	Lost to f/u:?		P 0.13	Risk of bias: 5/8	
	Follow up: 2y	23.5%F/U< 12 months.				
		Type of surgery: DAIR				

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Reference	Study design, setting and follow up	Study population characteristics	Intervention and control conditions	Outcome category	Results on primary and secondary outcomes + statistics	SIGN quality of evidence & Risk of Bias	Comments
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Tornero et al. 2014 [58]	Retrospective  Setting: multicentre 18 hospitals  Follow up: Med 722 days (range 168 – 1529)	subjects (n): I: n=127 C: n=51  Lost to follow up (n): 0  Type of surgery: DAIR, revision surgery.	I: Combination therapy.  C: Monotherapy.	Failure - defined as a situation in which inflammatory signs remained or reappeared during or after completing antibiotic treatment and/or the subject needed an unplanned surgery to control the infection.	Only the combination with rifampicin when administered in early infections (< 30 days after index surgery) was associated with a lower failure rate.  Failure rate 1: 57 (45%) C:	SIGN quality of evidence: 2- Risk of bias: 5/8	The duration of combination therapy was not defined.  Additional agents for combination treatment: aminoglycoside or rifampicin
Kheir et al. 2017 [57]	Retrospective  Setting: 3 institutions  Follow up: Range 1 – 12 years.	subjects (n): 87 I: not specified C: not specified  Lost to follow up (n): 0  Type of surgery: DAIR, revision surgery.	I: Combination therapy.  C: Monotherapy.	Failure: i) failed infection eradication, characterized by a fistula, drainage, pain or infection recurrence caused by the same microorganism strain, ii) subsequent surgical intervention for infection after reimplantation surgery, iii) PJI related mortality.	Treatment success: I versus C: P = 0.174, results not specified.	SIGN quality of evidence: 2- Risk of bias: 6/8	The duration of combination therapy was not defined.  Additional agents for combination treatment not specified.

Thompson et al. 2019 [61]	Retrospective Risk of bias: 6/8 Setting: regional analysis	subjects (n): 49 I: 8 C: 41 Lost to follow up (n): 0	I: Combination therapy.  C: Monotherapy.	Treatment success: at one year after the episode, a prosthetic joint was still in place without inflammatory signs or symptoms.	Treatment success: I: 100% C: 68% P 0.04	SIGN quality of evidence: 2-	Additional agents for combination treatment: rifampicin for > 2 weeks (range 19 – 200 days)
	Follow up: Minimum of 1 year.	Type of surgery: DAIR, revision surgery, no surgery.		Failure: chronic antimicrobial suppression therapy, permanent removal of implant, amputation, relapse or death from the infection. Reinfection with new pathogens was not considered as failure, and neither repeated surgical debridement to control the infection.			

Renz et al. 2019 [59]	Retrospective  Setting: 2 large orthopaedic hospitals  Follow up: Med 31.8 months (range 0.3 – 83.3)	subjects (n): I: n=59 C: n=15  Lost to follow up (n): 8  Type of surgery: DAIR, revision surgery, resection arthroplasty without reimplantation, no surgical intervention	I: Combination therapy.  C: Monotherapy.	Treatment success - defined as the absence of relapse or persistence of PJI due to enterococci or death related to enterococcal PJI	Treatment success: I: 73% C: 88% P=0.217	SIGN quality of evidence: 2- Risk of bias: 5/8	Additional agents for combination therapy: Fosfomycin, gentamicin, vancomycin or daptomycin.  The duration of IV combination therapy was not defined.

Table 4: Evidence table for PICO 4 (Gram negative bacilli)

Reference	Study design, setting and follow up	Study population characteristics	Intervention and control conditions	Outcome category	Results on primary and secondary outcomes + statistics	SIGN quality of evidence & Risk of Bias	Comments
Rodríguez- Pardo et al. 2014 [68]	Retrospective  Setting: multicentre (16 Spanish hospitals)  Median follow up time in months (IQR): 25 (15 – 39)	Subjects: I: n=124 C: n=15  Lost to follow up: n=0:  Type of surgery: DAIR	I: Ciprofloxacin C: Other antibiotic(s)	Failure: persistence or reappearance of inflammatory joint signs during follow-up, leading to unplanned surgery. Infection related death, a second debridement > 30 days after the first, prosthesis removal for any cause within the first 2 years of follow-up and need for suppressive antibiotic therapy was also considered as failure.	Treatment success: I: 79% C: 40% P=0.001	SIGN quality of evidence: 2- Risk of bias: 6/8	Ciprofloxacin was only compared with other regimens without specific data on the use of solely trimethoprimsulfamethoxazole.

Martínez- Pastor et al. 2009 [69]	Retrospective  Setting: single centre  Median follow up time in days (range): 463 (219 – 1090).	Subjects: I: n=28 C: n=19  Lost to follow up: n=0  Type of surgery: DAIR	I: Ciprofloxacin C: Other antibiotic(s)	Remission: during follow-up no symptoms of infection, the prosthesis was retained and the CRP was less than 1 mg/dL.  Failure: when inflammatory signs and a high CRP concentration remained during the treatment or reappeared after the subject completed treatment (relapse or reinfection).	Treatment success: I: 93% C: 47% P=<0.001	SIGN quality of evidence: 2- Risk of bias: 3/8	Ciprofloxacin was only compared with other regimens without specific data on the use of solely trimethoprimsulfamethoxazole.
Grossi et al. 2016 [72]	Retrospective  Setting: single centre  Minimal follow up time: two years after completion of antibiotic therapy	subjects: n= 76 I: n=58 C: n=18 Lost to follow up: n=0 Type of surgery: DAIR, revision surgery.	I: Ciprofloxacin C: Other antibiotic(s)	Treatment failure: requirement for further surgery and/or antibiotic administration due to relapse or persistence of infection or to a new infection during antibiotic treatment or after having completed it, or death related to infection or prolonged course of antibiotic suppressive therapy.	Treatment success: 1: 77.6% C: 83.3% P= 0.75	SIGN quality of evidence: 2- Risk of bias: 5/8	Ciprofloxacin was compared with IV beta-lactam with or without combined with another agent other than a fluoroquinolone.

## PICO 5a: no studies were included

 Table 5: Evidence Table for PICO 5b (Cutibacterium acnes)

Reference	Study design, setting and follow up	Study population characteristics	Intervention and control conditions	Outcome category	Results on primary and secondary outcomes + statistics	SIGN quality of evidence & Risk of Bias	Comments

Piggott et al.	Retrospective	Subjects: n=21	I: Rifampicin	Favourable outcome –	Favourable:	SIGN quality of	Conclusion: In this series,
2015 [77]	cohort study	I: n=15 (71.4%)	· · · · · · · · · · · · · · · · · ·	defined as an outcome	I: n=11/15 (73%)	evidence: 2-	treatment outcomes were
		C: n=6 (28.5%)	C: No rifampicin	where there was a	C: n=3/5 (60%)		comparable with and
	Setting:	T (D)		recorded improvement	P=0.61	Risk of bias: 4/8	without rifampicin therapy.
	single-centre	Type of PJI		in pain symptoms and			However, this drug was
		n=21 (100%) shoulder		functional performance			poorly tolerated and
	Median follow-	T		relative to a subject's			prematurely discontinued in
	up in months:	Type of surgery:		preintervention clinical			40% of cases. These findings
24	24	: 		status,			suggest the role for
		n=2 (13%) removal n=3 (20%) 1SR		without requirement for unplanned			rifampicin in the management of <i>C acnes</i> PJIs
		n=4 (27%) 2SR		additional surgical			requires further study.
		n=1 (6.7%) DAIR		debridement for			requires further study.
		n=5 (33%) none		putative persistent			Rifampicin doses:
		C:		infection.			not mentioned.
		n=1 (17%) removal		incetion.			not memorica.
		n=3 (50%) 2SR		The final clinical			Side-effects of rifampicin:
		n=2 (33%) none		outcome was			n=6 (40%) stopped using
		( /		determined as per the			rifampicin due to side-
		Median age in years		clinical status at the last			effects.
		(range): 62 (40-81)		recorded			
		I: not stated		clinical visit.			Antibiotic combinations:
		C: not stated					not mentioned.
		Male sex: n=19					
		I: not stated					
		C: not stated					
		LTFU: n=1 (4.8%)					
		I: n=0					
		C: n=1 (17%)					

Aydın et al. 2021 [43]	Meta-analysis  Setting: 2 single-centre observational studies (Piggott et al.2015 & Jacobs et al. 2015)  Follow-up time: not stated	Subjects: n=80 I: n=54 (67.8%) C: n=26 (32.5%) Type of PJI: Shoulder, knee, hip Type of surgery: - DAIR - Replacement surgery (numbers not stated) Mean/median age (years): not stated	I: Rifampicin C: No rifampicin	Failure - defined as death or relapse or recurrence of PJI.	Failure: I: n=8 (14.8%) C: n=5 (19.2%) RR 1.61 (0.58-4.47)	SIGN quality of evidence: 1+ Risk of bias: 13/14	NB: This systematic review includes the studies from Jacobs et al. and Piggott et al.  Conclusion: In the <i>C acnes</i> subsets, neither individual nor combined analysis favoured rifampicin-based regimens.  Rifampicin doses: not mentioned.
		Male sex: I: not stated C: not stated  LTFU: not stated					Side-effects of rifampicin: not mentioned  Antibiotic combinations: not mentioned.

Jacobs et al.	Retrospective	Subjects: n=60	I: Rifampicin	Failure of the retained	Failure	SIGN quality of	Conclusion: C acnes-
2015 [76]	cohort study	1: n=39	i. Kilallipicili	and replaced prosthesis	After 1 year	evidence: 2+	associated PJI treated with
2013 [70]	conort study	C: n=21	C: No rifampicin	after finishing	I: n=2/39 (5.1%)	evidence. 2+	surgery in combination with
	Setting:	C. 11–21	C. NO mampicin	antimicrobial treatment		Risk of bias: 5/8	long-term antibiotic
	Single-centre	Type of PJI:		was defined as a	C. 11–2/21 (9.5%) P=0.7	NISK OI DIAS. 5/6	administration
	Single-centre	l:			P-0.7		had a successful outcome at
	Follow-up:	- n=15 (38.5%) Knee		relapse, reinfection, and/or removal of the	After 2 years		1- and 2-year follow-up
	1 year and 2	- n=12 (30.8%) Hip		prosthesis for any	I: n=4/23 (17.4%)		irrespective of whether the
	years	- n=12 (30.8%)		reason.	C: n=3/13 (23.1%)		subject was treated with
	years	Shoulder		reason.	P=0.6		rifampicin.
		C:		A relapse was	7 -0.0		mampiem.
		- n=9 (42.9%) Knee		defined as positive	Relapse		Rifampicin doses:
		- n=6 (28.6%) Hip		cultures yielding the	After 2 years		450 mg 2x/day
		- n=6 (28.6%) Shoulder		same microorganism	I: n=2 (5.1%)		130 mg 2x, aay
		6 (26.676) 6.164.146.		as the initial	C: n=2 (9.5%)		Side-effects of rifampicin:
		Type of surgery:		intraoperative samples.	P=0.4		No (0%) subjects stopped
		l:		р.с.			using rifampicin due to side-
		- n=5 (12.8%) DAIR		A reinfection was	Reinfection		effects.
		- n=25 (64.1%) 1SR		defined	After 2 years		
		- n=9 (23.1%) 2SR		as a new infection with	I: n=2 (5.1%)		Antibiotic combinations:
		C:		another pathogen.	C: n=1 (4.8%)		Rifampicin was combined
		- n=1 (4.76%) DAIR			P=0.5		with clindamycin (n=33) or
		- n=16 (76.2%) 1SR					teicoplanin (n=6).
		- n=4 (19.0%) 2SR					In the control group most
							people received clindamycin
		Median age in years					(n=16). Other people got
		(range): 69 (40, 80)					amoxicillin (n=1),
		I: 69 (40, 78)					ciprofloxacin combined with
		C: 69 (47, 80)					clindamycin (n=1),
							doxycycline (n=1), linezolid
		Male sex: 31 (51.7%)					(n=1) or teicoplanin (n=1).
		I: n=17 (43.6%)					
		C: n=14 (66.7%)					
		LTFU:					
		- 1 year follow-up: n=0					
		(0%)					
		<ul><li>2 years follow-up:</li></ul>					
		n=24 (40%)					

Kusejko et al. 2021 [78]	Retrospective cohort study  Setting: Multicentre (9 countries, 18 centres)  Median follow-up in months (IQR): 36 (23-60)	Subjects: n=187 I: n=81 C: n=106  Type of PJI: I: - n=40 (49.4%) Hip - n=34 (42.0%) Shoulder - n=7 (8.6%) Knee - n=0 (0.0%) Other C: - n=57 (53.4%) Hip - n=36 (34.0%) Shoulder - n=10 (9.43%) Knee - n=3 (2.8%) Other  Type of surgery: I: - n=15 (18.5%) DAIR - n=31 (38.3%) 1SR - n=20 (24.7%) 2SR with spacer - n=12 (14.8%) 2SR without spacer - n=3 (3.7%) Explantation without new prosthesis C: - n=19 (17.9%) DAIR - n=20 (18.9%) 1SR - n=43 (40.3%) 2SR with spacer - n=20 (18.9%) 2SR without spacer - n=20 (18.9%) 2SR without spacer - n=4 (3.8%) Explantation without	I: Rifampicin C: No rifampicin	Treatment failure - defined as either infection relapse, new infection, or death from PJI.  Infection relapse - defined as proven when persisting signs or symptoms of infection (pain, swelling, redness, wound secretion, or elevated serum inflammatory parameters) were present and 2 new diagnostic samples microbiologically identified the same <i>C acnes</i> . Defined as possible when not microbiologically proven but suggested by persisting symptoms or signs of infection.  New infection - defined as a microbiologically proven infection in case of a new pathogen detected in ≥2 diagnostic samples during the follow-up period.	Overall Failure I: n=10 (12.3%) C: n=28 (26.5%) P=0.0288  Relapse proven and possible I: n=8 (9.9%) C: n=20 (18.9%) P=0.1334  New Infection I: n=2 (2.5%) C: n=11 (10.4%) P=0.0692  Death I: n=4 (4.9%) C: n=9 (8.5%) P=0.5116  Treatment failure and the addition of rifampicin: adjusted HR=0.5, P=0.07	SIGN quality of evidence: 2+ Risk of bias: 5/8	Conclusion: When adjusting for surgical strategy and overall duration of antibiotic treatment, the effect of adding rifampicin was not significant. However adjusting for DAIR (instead of surgical strategy) and duration of the antibiotic treatment did result in a statistically significant effect of adding rifampicin.  Rifampicin doses: - 44.4% 450 mg 2x/day - 27.8% 600 mg 1x/day - 33.3% no doses recorded  Side-effects of rifampicin: not mentioned  Antibiotic combinations: Rifampicin was combined with clindamycin (n=29), fluoroquinolone (n=32), amoxicillin or amoxicillin/clavulanate (n=19), tetracycline (n=4), or other antibiotics (n=2). Therapy without rifampicin consisted of clindamycin (n=48), amoxicillin (n=46), tetracycline (n=4), or other antibiotics (n=26).
		new prosthesis					

Median age in years (IQR): 67 (58, 74) I: 65 (57, 72) C: 68 (59, 76)

Male sex: n=135 (72.2%) I: n=60 (74.1%) C: n=75 (70.8%)

LTFU: 0 (0%)

Abbreviations: % = percentage;  $\ge$  = larger than or equal to; 1SR = one-stage revision; 2SR = two-stage revision; C = control group; DAIR = Debridement, Antibiotics and Implant Retention; I = intervention group; IQR = interquartile range; LTFU = lost to follow-up; n = number; P = p-value; PJI = prosthetic joint infection

Table 6: Evidence Table for PICO 6 (Candida)

Reference	Study design, setting and follow up	Study population characteristics	Intervention and control conditions	Outcome category	Results on primary and secondary outcomes + statistics	SIGN quality of evidence & Risk of Bias	Comments

Kim et al. 2015 [82]	Systematic review  Setting: 20 articles included  Mean follow up time in months: 34	Subjects n=37 I: n=6 C: n=9  Mean age in years: 65  Male sex: 16 (43%)  Lost to follow up: not mentioned  Type of surgery: Removal of the prosthesis n=32 (87%) DAIR n=2 None n=3  Type of joint: Hip n=37 (100%)	Sub analysis: I: THA reimplantation with antifungals impregnated cement spacer C: THA reimplantation without (impregnated) cement spacer	Relapse rate of Candida spp. infection	Relapse rate of Candida spp. infection I: n=0 (0%) C: n= 1 (11%) P=0.606; OR: 0.889 95%CI: 0.168-4.701	SIGN quality of evidence: 2- Risk of bias: 4/8	hypothesis was that staged reimplantation of a total hip prosthesis after Candida spp. infection is a reliable procedure providing symptomatic relief and successful outcomes.  Articles from retrospective, cross-sectional studies, clinical registries, or prospective studies were included Lack of prospective randomized studies No meta-analysis conducted due to the heterogeneity of the reports
							All subjects were treated with systemic antifungal medication therapy for various duration after the surgical procedure or primary therapy without surgical procedures (range, 4 weeks—indefinite, median 6 weeks) Fluconazole, amphotericin B, caspofungin, 5-flucytocine, ketoconazole, itraconazole or a combination of these antifungals.  Since echinocandin has significant fungicidal activity against Candida spp. with favourable safety

profile [30] and possible superiority over fluconazole for candidemia [43], primary use of echinocandin needs to be considered in cases of Candida spp. prosthetic hip joint infection complicated with severe candidemia sepsis

Limitations:

collected series with relatively short-term followup, and the retrospective design means diagnostic criteria, surgical approaches (e.g., posterior vs. lateral), medical managements, and postoperative rehabilitation were not completely standardized. A pooled analysis of a large international administrative database that was not designed for the clinical research. Therefore, potentially useful and more

detailed information was not available that could help further elucidate the outcomes of Candida spp. infection after THA Outcomes from older collected cases when newer antifungal therapy (for example, echinocandin, etc.,) was not available might have been different

in comparison with those of recently collected cases.

Koutserimpas et al.	Literature review	subjects (83): I: n=44 (53%)	Sub analysis: I: 2SR	Success rate - not defined	Success rate I: 96%	SIGN quality of evidence: 2-	C.parapsilosis is the predominant pathogen.
2019 [83]	Setting: included	C: n=8 (9.6%)	C: 1SR		C: 73%		MIC's for echinocandins are
	case-studies				P=0.023	Risk of bias: 5/8	usually elevated and were
	regarding the	Mean age in years (SD):					not used. <i>C. glabrata</i> is
	management of	66.3 (10.2)					usually resistant to azoles
	non-albicans						and only a limited number
	Candida PJIs	Male sex: n=36 (43,4%)					of cases was treated with
	through april						azole monotherapy.
	2018	Lost to follow up: n=7					No comparison was made
		(all underwent					of the success rate between
	Mean follow up	resection arthroplasty)					the different antifungals
	time in months						because of this.
	(SD): 33.3 (19.6)	Type of surgery:					Antifungal susceptibility
		2SR n=44 (53%)					knowledge and testing is
		Resection arthroplasty					therefore essential.
		n=18 (22%)					Echinocandins are the most
		1SR n=8 (9.6%)					recently developed
		Arthrodesis n=5 (6%)					antifungal agents. These
		DAIR n=3 (3.6)					agents have
		Amputation n=2 (2.4%)					immunomodulatory
		none n=3 (3.6%)					properties and can
		<del>-</del>					penetrate biofilms. No data
		Type of joint:					on superior clinical efficacy.
		Knee n=52 (62.6%)					
		Hip n=29 (35%)					
		Shoulder n=2 (2.4%)					

**Table 7**: Evidence Table for PICO 7 (Culture negative)

Refe	rence	Study design, setting and follow up	Study population characteristics	Intervention and control conditions	Outcome category	Results on primary and secondary outcomes + statistics	SIGN quality of evidence & Risk of Bias	Comments

Tirumala et al. 2020 [111]	Retrospective cohort study  Setting: single-centre  Median follow up time in years (range): I: 5.7 (3.5-9.8) C: 6.1 (3.9-10.5)	Subjects: n=149 I: n=46 C: n=103  Type of PJI: I: - n=20 hip (43%) - n=26 knee (57%) C: - n=39 hip (38%) - n=64 knee (62%)  Type of surgery: n=149 (100%) DAIR with modular component exchange  mean age in years (SD): I: 66.9 (9.6) C: 66.3 (10.4))  Male sex: 76 n= (%) I: n=22 (48%) C: n=54 (52%)  Lost to follow up: n=0	I: culture negative C: culture positive	Reinfection - not defined  Aseptic failure - not defined	Reinfection I: n=6 (13%) C: n=20 (19.4%) P=0.48  Aseptic failure I: n=4 (8.7%) C: n=5 (4.9%) P=0.46  Mean survival time from reinfection in years (SD) I: 7.7 (0.4) C: 7.4 (0.3) P=0.40	Risk of bias: 4/8 SIGN quality of evidence: 2-	Does not compare type of antibiotics used in culture negative group.  Conclusion: Despite lack of an identifying organism to guide postoperative antibiotic therapy, DAIR with modular component exchange for acute culture-negative PJI was associated with similar reinfection rates compared to acute culture-positive PJI, suggesting that culture negativity may not be a contraindication to DAIR in subjects with acute PJI.  IIV Antibiotics in intervention group: (all during 6 weeks) > n=44 subjects: vancomycin and cefepime. > n=2 (4.3%) monotherapy vancomycin

2012 [112]	Retrospective cohort study  Setting: single-centre	Subjects: n=175 I: n=40 C: n=135	I: culture negative	Treatment success- defined as subjects who	Treatment success I: n=34 (85%)	Risk of bias: 4/8	Does not compare type of
2012 [112]	cohort study Setting:		J	•	I: n=34 (85%)		
	U	C: n=135	_		5- (55/6)		antibiotics used in culture
	U			did not receive any	C: n=83 (61%)	SIGN quality of	negative group.
	single-centre		C: culture	additional surgical		evidence: 2-	
		Type of PJI:	positive	procedure for	Treatment failure		Conclusion: The success
		l:		persistent or recurrent	I: n=6 (15%)		rate of infection control
	Mean follow-up	- n=20 hip (50%)		infection after initial	C: n=52 (39%)		was higher in the culture-
	time in months	- n=20 knee (50%)		surgical treatment			negative group (p=0.006),
	(range):	C:			P=0.006		which suggests that
	58 (24-26)	- n=77 hip (57%)		Treatment failure -			culture negativity may not
		- n=58 knee (43%)		defined as subjects who			necessarily be a negative
				necessitated any			prognostic factor for
		Type of surgery:		additional surgical			periprosthetic joint
		n=56 DAIR		procedure for infection			infection.
		n=110 2SR		control.			
		n=7 reimplantation					IV Antibiotics in
		n=2 arthrodesis					intervention group:
							- Vancomycin n=28 (70%)
		Mean age in years (SD):					- Others n=12 (30%)
		I: 63.9 (10.5)					
		C: 65.9 (11.7)					Includes around 60% of
							chronic PJI.
		Male sex:					
		I: n=24 (60%)					
		C: n=65 (48%)					
		Lost to follow up: n=25					

Huang et 2012 [90]	al. Retros cohort Setting single-	g:	Subjects: n=343 I in 298 subjects I: n=48 I/subjects C: n=295 I in 250 subjects	I: culture negative C: culture positive	Infection control - was defined as the preservation of the prosthesis in the index joint without any further surgery related	Infection control I: n=37 (73%) C: 73% P=1.00	Risk of bias: 4/8 SIGN quality of evidence: 2-	Discussion: Our higher infection control rates with vancomycin compared with other parenteral antibiotics suggest that vancomycin-
	time ir (range I: 47 (1	follow-up n months ): 12-119) 2 (12-125.7)	Type of PJI: I: - n=21 hip (38%) - n=28 knee (51%) C: Not mentioned		to infection.	Survival Kaplan Meier shows similar infection- free survival between I and C after I&D (P=0.73) and 2SE (P=0.96)		sensitive gram-positive organisms may still be the most common culprit in culture-negative infections.
			Mean age in years (range): I: 63.7 (39-85) C: 66.7 (18-89)			n=11 (28.2%) of I who were treated with vancomycin failed treatment.		IV Antibiotics in intervention group: n=39 minimum of 4 weeks vancomycin iv > sometimes combined with ciprofloxacin iv (n=2),
			Male sex: I: 19 (40%) C: 122 (49%) Lost to follow up: n=25					ciprofloxacin po (n=4), doxycycline iv (n=1), rifampicin po (n=1), ceftriaxone iv (n=1), vancomycin po (n=1) n=4 ceftriaxone
			Type of initial surgery: I: n=12 (25%) I&D n=33 (69%) 2SR n=3 (6%) 1SR					n=1 ceftazidime n=1 daptomycin and oral ciprofloxacin n=1 nafcillin iv n=1 no antibiotics
			C: n=85 (29%) I&D n=205 (69%) 2SR n=2 (0.6%%) 1SR n=1 (0.3%) fusion n=1 (0.3%) amputation n=1 (0.3%) tot femur					
			prostalac					

Ibrahim et al. 2018 [87]	Prospective cohort study	Subjects: n=100 I: n=50	I: culture negative	Re-infection	Re-infection I: n=3 (6%)	Risk of bias: 3/8	Does not compare type of antibiotics used in culture
2010 [07]	conort study	C: n=50	ricgative	The eradication of	C: n=3 (6%)	SIGN quality of	negative group.
	Setting:	C. 11–30	C: culture	infection is defined as	P=0.19	evidence: 2+	negative group.
	single-centre	Type of PJI:	positive	the absence of clinical,	. 0.25	CVI.0011001 2	IV Antibiotics in
	0 - 1 - 1	n=100 (100%) hip		serological, and			intervention group: not
	Mean follow-up	, , ,		radiographic signs at			mentioned
	time in years:	Type of initial surgery:		any subsequent time.			
	minimum 5 years	n=100 (100%) 2SR		The Musculoskeletal			
				Infection Society (MSIS)			
		n=100 (100%) chronic		criteria were used at			
		infection		the final review to			
				confirm the control of			
		Mean age in years		infection. Failure was			
		(range):		defined as any major			
		I: 74 (43-88)		operation performed in			
		C: 71 (41-83)		any subject for the			
				control of infection,			
		Male sex:		including further two-			
		I: 23 (%)		stage revision, excision			
		C: 21 (%)		arthroplasty,			
		Lost to follow up: n=8		arthrodesis,			
		Lost to follow up: fi=8		amputation or the need for long-term antibiotic			
				suppression.			
				34ppi 6331011.			

Reisener & Perka	Systematic review	Subjects: n=3342 I: n=504	I: Culture negative	Incidence rate of culture negative PJI	Overall incidence rate estimate of culture	Risk of bias: 10/14	Does not compare outcomes between type of
2018 [88]		C: n=		among subjects with PJI	negative PJI among		antibiotics used in culture
	8 included		C: Culture		subjects with PJI (95%	SIGN quality of	negative group.
	studies	Type of PJI	positive	Antibiotics used	CI): 11% (10-12)	evidence: 1-	
	Median follow-up	I: 36% hip		Successful treatment	IV Antibiotics in		Conclusion: vancomycin is used most often. It is
	time in months,	64% knee		Successiui treatment	intervention group,		unclear what the best
	range: 36-127.2	0470 KIEC			range:		treatment option is.
	14.1861.00 127.12	Type of surgery:			- 12-70% vancomycin		ti catimoni option isi
		l:			- 0-33% vancomycin +		
		n=283 (56%) 2SR			ceftriaxone		
		n=137 (25%) DAIR			- 0-10% cephalosporins		
		n=16 (3%) 1SR			- 6-34% other		
		n=42 (8%) permanent					
		resection			Successful treatment in		
		n=26 (5%) chronic			I group, range:		
		suppression with antibiotics			85-95%		
		antibiotics					

Santoso et al. 2018 [86]	Retrospective cohort study  Mean follow-up time in months (range): I: 29.5 (12-78) C: 30.9 (12-71)	Subjects: n=84 I: n=27 C: n=57  Type of PJI: n=84 (100%) hip  Type of surgery: n=84 (100%) intended 2SR (n=6 followed different pathway in the end due to varying circumstances)  Mean age in years (range): I: 67.4 (40–85) C: 67.3 (36–84)  Male sex: I: 15 (55.%) C: 30 (52.6%)  LTFU: n=10	I: Culture negative  C: Culture positive .	Infection control - not defined  Infection recurrence - not defined	Infection control I: n=25 (92.6%) C: n=47 (82.4%) P=0.21 Infection recurrence I: n=2 (7.7%) C: n=8 (15.4%)	Risk of bias: 3/8 SIGN quality of evidence: 2-	Does not compare outcomes between type of antibiotics used in culture negative group within own study population.  Conclusion: vancomycin was only used in 29.6% of culture-negative subjects in order to reduce the risk of future bacterial resistance. This decision still resulted in a reasonable treatment outcome in the culture-negative group.  An extensive utilisation of parenteral vancomycin in culture-negative PJI may, therefore, be unwarranted and further study is needed.  IV Antibiotics in intervention group: n=23 (85.2%) cephalosporin n=8 (29.7%) vancomycin n=2 (7.4%) ciprofloxacin

Wang et al. 2018 [89]	Retrospective cohort study  Setting: single-centre  Median follow-up time in months (IQR): 68.5 (41-97.3)	Subjects: n=58 I: n=19 C: n=39  Type of PJI: n=58 (100%) hip  Type of surgery: n=58 (100%) intended 2SR (n=10 (17.2%) followed different pathway in the end due to varying circumstances)  Mean age in years (range): 65.4 (36-86) I: 61 (50-75) C: 69 (60-76)  Male sex: I: n=8 (42%) C: n=21 (54%)  LTFU: n=0 (0%)	I: Culture negative  C: Culture positive	Re-infection - not defined	Re-infection: n=4 (6.9%) I: n=0 (0%) C: n=4 (10.2%) P=0.397  Risk factors influencing re-infection from univariate coxregression analysis: - Sinus secretion culture-positive HR (95% CI) 11.08 (1.13-108.89) P=0.039	Risk of bias: 3/8 SIGN quality of evidence: 2-	Does not compare outcomes between type of antibiotics used in culture negative group.  IV Antibiotics in intervention group: I: rifampicin and levofloxacin.

Yoon et al. 2017 [85]	Systematic review 7 included studies	Subjects: n=495  Type of PJI: hip and knee (numbers not mentioned)	No intervention/control group  All subjects: culture negative	Prevalence of culture negative PJI in subjects with PJI.  Major risk factors for	Prevalence of culture negative PJI in subjects with PJI, range: 0%- 42.1%	Risk of bias: 6/14 SIGN quality of evidence: 1-	Does not compare outcomes between type of antibiotics used in culture negative group.
	Mean follow-up time not mentioned	Type of surgery: 2SR, DAIR, 1SR, permanent resection	PJI	CN PJI  Antibiotics used	Major risk factors for CN PJI: - prior antibiotic use - presence of postoperative wound		No quality assessment of included studies; statements are rarely supported by numbers.
		Mean age in years: not mentioned Male sex: not mentioned			drainage.  IV Antibiotics, range: - Glycopeptide 12-100% - Cephalosporins 10- 82%		Conclusion: further studies are needed to establish standard diagnostic methods for identifying infecting organisms and treatment
		Lost to follow up: not mentioned			- Other 6-30%		strategies for CN PJI.

Abbreviations: % = percentage;  $\ge$  = larger than or equal to; 1SR = one-stage revision; 2SR = two-stage revision; C = control group; DAIR = Debridement, Antibiotics en Implant Retention; I = intervention group; IQR = interquartile range; LTFU = lost to follow up; IQR = number; I = prosthetic joint infection

 Table 8: Evidence Table for PICO 8 (Suppressive Therapy)

setting and characteristics control secondary outcomes + evidence follow up conditions statistics & Risk of Bias	Reference	_	Study population characteristics		Outcome category	•		Comments
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Escudero- Sanches et al. 2020 [113]	Retrospective case series with embedded case-control study  Setting: Multicentre (29 hospitals)  Follow-up in months: minimum 6 months	Subjects: n=302 Cases: n=125 (41.4%) Controls: n=177 (58.6%)  Type of PJI: n=157 (52%) knee n=136 (45.0%) hip n=9 (3.0%) upper limb  Type of management: Cases: n=11 debridement with partial removal n=56 debridement without removal n=56 non-surgical Controls: n=13 debridement with partial removal n=87 debridement without removal n=87 debridement without removal n=76 non-surgical  Mean age in years (SD): Cases: 74.3 (13.9)  Controls: 76.3 (13.9)  Male sex: Cases: n=51 (41.8%) Controls: n=71 (58.2%)	Cases: SAT failure - was indicated by the appearance or persistence of a fistula, the need for debridement or replacement of the prosthesis due to persistence of the infection or the presence of uncontrolled symptoms.  Controls: SAT success - cases in which none of the above described events occurred.	Age Type of microorganism Location of PJI	Median duration of SAT in months (IQR): 36.5 (20.75-59.21)  Multivariate analyses; variables that are associated with SAT failure: - Age > 70 years P=0.013 - Other microorganism than gram-positive cocci P=0.025 -PJI in the upper limb. P=0.000	SIGN quality of evidence: 3 Risk of bias:	Among the possible causes for the failure of SAT, the reported causes were the suspension of SAT in 21/125 subjects (16.8%)

eijtens et al.	Retrospective case series	Subjects: n=23	N/A	SAT successful - cases with retention of the	The mean duration of	SIGN quality of evidence: 3
019 [114]	case series	Mean age in years		prosthesis without	SAT in months (range): 38 (1-151)	evidence: 3
	Setting: single-	(range): 70 (40-88)		clinical relapse of	SAT successful: n=13	Risk of bias:
	centre	Type of PJI:		infection at final	(56.5%)	
		n=21 (91.3%) total hip		follow-up.		
	Median follow-	arthroplasty				
	up in months: 33	n=2 (8.7%) hemiarthroplasty		Failure - was defined as death		
		nemial till Opiasty		related to PJI or new		
		Type of surgery:		surgical intervention at		
		n=13 (56.5%) DAIR		prosthesis side due to		
		n=7 (30.4%) partial or		persistent or recurrent		
		total revision		infection.		
		n=3 (12.5%) non- surgical				
		Jurgicur				
		Male sex: 7 (30.4%)				
		Mean age in years (SD):				
		Cases: 74.3 (13.9)				
		Controls: 76.3 (13.9)				

Malahias et al. 2020 [121]	Systematic review Included studies: 7 Mean follow-up per study in years, range: 2.3-5	Subjects: n=424 (treated with SAT and DAIR)  Type of PJI: hip, knee, elbow, shoulder  Type of surgery: n=437 (100%) DAIR  Male sex: 71.6%  Mean age per study in years, range: 61.7-66 years	N/A	Infection free All-cause re-operation Adverse effects associated with long-term antibiotic use	Infection free n=318/424 (75%) All-cause re-operation: n=12/178 (6.7%) Adverse effects associated with long- term antibiotic use: n=29/188 (15.4%)	SIGN quality of evidence: 1- Risk of bias:	Conclusion: The results of this systematic review demonstrate that there is still only low-quality evidence regarding the therapeutic effect of DAIR combined with SAT, which is not enough to draw definitive conclusions.

Pavoni et al. 2004 [91]	Retrospective case series	Subjects: n=34  Type of PJI: n=24 hip	N/A	improvement with no relapse Improvement with	Mean duration of antimicrobial therapy 41.2 weeks	SIGN quality of evidence: 3 Risk of bias:	Limitations: retrospective nature, the fact that the subject population was not
	Mean follow-up in months	n=10 knee		early relapse = relapse after initial	improvement with no relapse n=17		homogeneous, and the wide ranges in duration of
	(range) for subjects with no	Type of surgery: n=13 debridement		improvement after <6 months of stopping	Improvement with		therapy and follow-up.
	relapse: 22 (9-57)	Male sex: n=7		antibiotics	early relapse: n=7		
		Age in years, range (mean/median not		Improvement with late relapse = relapse after	Improvement with late relapse: n=3		
		mentioned): 43-86		initial improvement after >6 months of	Side-effects of SAT		
		LTFU: n=2		stopping antibiotics	requiring discontinuation: n=0		
				Side-effects of SAT requiring			
				discontinuation			

Type of PJI:  Setting: single- centre  n=37 (47%) knee n=2 (3%) shoulder in days (SD):  1020 (597)  Type of surgery: n=59 (75.6%) DAIR n=19 1SR or 2SR Male sex n=34 (43.6%) Mean age in years (SD): 64.1 (16.8)  Type of PJI: infection assessed at least 24 months after the end of the curative the end of the curative treatment and then at the last contact with the subject.  SAT discontinuation: n=14 (18%)  SAT discontinuation: n=14 (18%)  SAT discontinuation: n=6 (8%)  SAT discontinuation: n=6 (8%)  Adverse events likely attributable to SAT  SAT discontinuation: SAT in subjects with PJI  Adverse events likely attributable to SAT: n=14 (18%)  SAT discontinuation: n=6 (8%)  SAT discontinuation: SAT discontinuation: N=14 (18%)  Adverse events likely attributable to SAT  SAT discontinuation	Setting: single- centre	Pradier et al. 2018 [116]	Retrospective case series	Subjects: n=78	N/A	Remission - defined as the absence of signs of	Failure: n=22 (28.3%)	SIGN quality of evidence: 3	Aim: to describe the use of oral tetracyclines as
attributable to SAT	attributable to SAT		centre  Mean follow-up in days (SD):	n=37 (47%) knee n=2 (3%) shoulder n=4 (5%) elbow Type of surgery: n=59 (75.6%) DAIR n=19 1SR or 2SR Male sex n=34 (43.6%) Mean age in years (SD):		the end of the curative treatment and then at the last contact with the subject.  Failure - defined as any other outcome including death except when it was not in relation with the PJI.	attributable to SAT: n=14 (18%) SAT discontinuation:	Risk of bias:	SAT in subjects with PJI
SAT discontinuation	SAT discontinuation					attributable to SAT			
						3.11 discontinuation			

Prendki et al. 2017 [115]	Case series  Setting: multicentre (27 centres in France)  Median follow- up in months: 6.3	Subjects: n=136  Type of PJI: n=81 (59.6%) hip n=53 (39%) knee n=2 (1.5%) shoulder  Type of surgery: n=79 non-specified surgery n=57 none	N/A	Occurrence of event - defined as: (i) local or systemic progression of the infection (failure), (ii) death and (iii) discontinuation or switch of PSAT	Occurrence of an event: n=46 (33.8%) - Progression of sepsis: n=8 (5.8%) - Death: n=13 (9.6%) - Adverse drug reaction leading to definitive discontinuation or switch of PSAT: n=25 (18%)	SIGN quality of evidence: 3 Risk of bias:	Subjects >= 75 years
		Median age in years (IQR): 83 (81-88)  Male sex: 64 (47.1%)			Survival rate without an event after 2 years (95% CI): 61% (51-74)		

Prendki et al. 2014 [117]	Retrospective case series	Subjects: n=38	N/A	Failure - defined as persisting infection,	Failure: n=6 - Persisting infection:	SIGN quality of evidence: 3	Subjects >=80 years
		Type of PJI:		relapse, new infection,	n=1		
	Setting: single-	n=24 (63%) hip		treatment	- Relapse: n=3	Risk of bias:	
	centre	n=13 (34%) knee		discontinuation due to	- Related death: n=1		
		n=1 (%) shoulder		severe adverse events,	- SAT was stopped due		
	Median follow-			and related death.	to side effects: n=1		
	up in months	Type of surgery:					
	(range): 24 (6-98)	n=6 (16%) synovectomy		Persisting infection -	Death from an		
		n=3 (8%) abscess		defined as persistence	unrelated cause: n=9		
		drainage		of clinical signs of PJI.			
		n=1 (3%) partial					
		exchange		Relapse - defined as			
		n=1 (3%) excision of		reappearance of			
		fistula		clinical signs of PJI after			
		n=29 (76%) none		a symptom-free			
				period if the same			
		Median age in years		bacterial organism was			
		(range): 84 (80-95)		isolated as was found			
				at inclusion.			
		Male sex n=17 (45%)					
				New infection -			
		LTFU: not mentioned		defined as			
				reappearance of			
				clinical signs of PJI after			
				a symptom-free			
				period if another			
				bacterial organism was			
				isolated as was found			
				at inclusion.			
				Deaths unrelated to PJI			

Rao et al. 2003 [118]	Prospective case series  Setting: single centre  Mean follow-up in months (range): 61.5 (16-128)	Subjects: n=36  Type of PJI: n=15 (42%) hip n= 19 (53%) knee n=2 (5.5%) elbow  Type of surgery: n=36 (100%) DAIR  Mean age in years (range): 77 (62-96)  Male sex: n=19 (53%)  LTFU: not mentioned  Mean duration of SAT treatment in months (range): 52.6 (6-128)	N/A	Treatment failure - defined as the development of progressive pain, loosening of the implant, or drainage despite antibiotic therapy.  Complications related to antibiotic therapy	Treatment failure n=5 (14%)  Duration of SAT (and number of treatment failures): - 6 months n=1 (n=0) - 7-12 months n=3 (n=1) - 13-24 months n=8 (n=2) - >24 months n=24 (n=2) - > All treatment failures happened while subjects were still using SAT.  Complications related to antibiotic therapy: n=3 (8%)	SIGN quality of evidence: 3 Risk of bias:	Conclusion: The ideal regimen and optimal duration of oral suppressive therapy for a favourable outcome is not well-established and needs additional data with prospective multicentre studies.

Wouthuyzen-	Retrospective	Subjects: n=21	N/A	Failure - defined as	Failure:	SIGN quality of
Bakker et al.	case series	Subjects. II-21	14//	subjects who still	n=7 (33%)	evidence: 3
2017 [120]	0.000 00.100	Type of PJI:		experienced joint pain,	/ (55/5)	21142113213
	Setting: Single	n=13 (62%) hip		when surgical	Treatment success:	Risk of bias:
	centre	n=6 (29%) knee		intervention	Standard prosthesis:	
		n=2 (10%) shoulder		(debridement,	90%	
	Median follow-	( ,		removal, arthrodesis or	Tumor prosthesis: 50%	
	up in months	Type of surgery:		amputation) was	'	
	(range): 21 (3-81)	n=3 (14%) DAIR		needed to control the	Side-effects of	
		n=8 (38%) lavage		infection	antibiotics: 43%	
		n=3 (14%) DAIR + lavage		and/or when death		
		n=1 (5%) reposition		occurred due to the		
		n=1 (5%) excision		infection.		
		sarcoma				
		n=5 (24%) None				
		Median age in years				
		(range): 67 (21-88)				
		Mean duration SAT: not				
		mentioned (probably				
		entire follow-up time)				
		Excluded subjects:				
		n=3/24				

**Table 9:** Evidence Table for PICO 9a and 9b (duration of antibiotic course)

Reference	Study design, setting and follow up	Study population characteristics	Intervention and control conditions	Outcome category	Results on primary and secondary outcomes + statistics	SIGN quality of evidence & Risk of Bias	Comments
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Chieffo et al. 2020 [104]	Retrospective case series  Setting: single-centre  Median follow- up time in months (IQR): 32 (12-101)	Subjects: n=50  Type of PJI: - n=42 hip (84%) - n=8 knee (16%)  Type of surgery: 50 (100%) 1SR  Median age in years (IQR): 69.3 (24.5, 97.4)  Male sex: n=31 (62%)  LTFU: n=1 (2%)	No intervention/control group  All subjects were treated with 6 weeks of antibiotics after 1SE.	Remission – defined as the absence of local and systemic signs of PJI during the follow-up (minimum 1 year after the end of treatment).  Failure – included relapse and new infections after treatment completion.  Relapses with the same microorganism	Remission n=44/49 (90%) total n=37/41 (90%) hip n=7/8 (88%) knee  Failure n=5 (10%)  Relapses with the same microorganism n=4 (8.2%)  New infection: n=1 (2.0%)	SIGN quality of evidence: 3 Risk of bias:	Conclusion: a six-week course of antibiotics in knee and hip PJIs treated with 1SR has a satisfactory remission rate in this open study.
				New infection			

Bene et al. 2018 [103]	Retrospective case-control study  Setting: single-centre  Median follow-up time in years (range): 4.1 (0.4–7.7)	Subjects: n=26 Cases: n=2 Controls: n=24  Type of PJI: - n=26 hip (100%)  Type of surgery: - I&D with head and liner exchange  Mean age in years (SD): 61.7 (10.7)  Male sex: nog stated	No intervention/control group but comparison of group with and without reoperation-free survival.  Cases: subjects with a reoperation for infection recurrence during follow-up time.	Reoperation for infection recurrence - as defined by MSIS criteria.  Weeks of antibiotics use	Weeks of antibiotics use (mean, SD): 64.2 (66.8) - Cases: 64.2 (66.8) - Controls: 96.4 (115.3) P=0.8639  Multivariate analysis of risk of reoperation for infection using the predictor "weeks of antibiotic use": HR (95% CI) 0.997 (0.993–0.999) P=0.0333	SIGN quality of evidence: 2- Risk of bias:	Conclusion: Chronic antibiotic suppression should be considered following THA I&D with head and liner exchange.
		LTFU: 0 (0%)	Controls: subjects without a reoperation for infection recurrence during follow-up time.		F - 0.0333		

Benkabouche et al. 2019 [124]	RCT Setting: single-centre, 2SR Median follow- up in years: 2.2	Subjects n=123 I: n=62 C: n=61  Types of infection and surgery: NB: NOT ONLY PJI n=39 (32%) 2SE for prosthetic joint infection n=44 (36%) metal plate infection n=11 (9%) intramedullary nail infection n=30 (24%) infection of other osteosynthesis  Median age in years: 64  Male sex: 38 (62%) I: n=17 (43.6%) C: n=14 (66.7%)	I: 4-weeks antibiotics C: 6-weeks antibiotics	Remission  — defined as the complete absence of clinical, laboratory or radiological findings that would indicate the persistence of infection after a minimal follow-up of 6 months after treatment.  Significant antibiotic-related adverse events  — Not defined  .	Intention to treat analysis:  Remission I: n=58 (95%) C: n=58 (94%) P=0.71  Significant antibiotic- related adverse events I: n=17 (28%) C: n=22 (35%) P= 0.36  Per protocol analysis: Remission I: 57 (95%) C: 54 (95%) P=0.95  Significant antibiotic- related adverse events I: 17 (28%) C: 19 (33%)	SIGN quality of evidence:1+ Risk of bias: 8/10	Conclusion: no statistically significant difference in the rates of clinical or microbiological remission between subjects randomized to only 4 compared with 6 weeks of systemic antibiotic therapy after removal of an infected osteoarticular implant.  Study is about 2SR, not about DAIR or 1SR (amongst other non PJI infections)
		C: n=14 (66.7%)			related adverse events I: 17 (28%)		

C: 3 (4.9%)

Chaussade et al.	Retrospective	Subjects: n=87	I: 6 weeks	Remission - defined as:	Remission	SIGN quality of	Conclusion: In subjects
2017 [96]	cohort study	I: n=44	antibiotics	1) the absence of	n=60 (69%)	evidence: 2-	undergoing DAIR for hip
		C: n=43		clinical, imaging and	I: n=31 (70.45%)		or knee PJI, the likelihood
	Setting:	T (D)	C: 12 weeks	biological (i.e.,	C: n=29 (67.44%)	Risk of bias: 5/8	of long-term remission
	multicentre	Type of PJI:	antibiotics	inflammatory markers)	12 weeks vs. 6 weeks		Was
	Mean follow-up	l: n=31 (70.45%) hip		signs of infection after a minimum follow-up	antibiotics		not significantly different for those receiving 6
	time in months:	n=23 (29.55%) knee		period of 12 months	- Unadjusted OR (95%		versus 12 weeks of
	52.1	C:		after surgery; and, 2)	CI): 0.87 (.35–2.16)		antibiotic therapy.
		n=29 (67.44%) hip		no need for continuing	P=0.76		Prospective RCT's are
		n=14 (32.56%) knee		antibiotic therapy, e.g.	- Adjusted OR (95% CI):		required to confirm this
		_		for suppressive	0.76 (0.27-2.10),		observation.
		Type of surgery:		treatment.	<i>P</i> =0.60		
		n=87 (100%) DAIR					
		Median age in years: 71					
		(IQR not mentioned)					
		l: 71					
		C: 71					
		Male sex: n=45 (51.72%)					
		I: n=24 (54.55%)					
		C: n=21 (48.84%)					
		LTFU: 28 (was an					
		exclusion criterion)					

El Helou et al. Retrospecti 2011 [123] cohort stud	I: n=82	I: 4 weeks iv antibiotics	Treatment failure - defined by one of the	From the Cox Proportional Hazards	SIGN quality of evidence: 2-	Conclusion: Six weeks of parenteral antimicrobials
Setting: single-centr 2SR  Mean follow time in year (SD): I: 6.6 (10.3) C: 4.5 (2.8)	I: n=36 (43.9%) hip -up n=46 (56.1%) knee	C: 6 weeks iv antibiotics	following criteria: (1) recurrence of prosthetic joint infection caused by the same strain of microorganism or a different microorganism at any time after reimplantations surgery; (2) death caused by prosthesis- related infection at any time after reimplantation surgery; (3) clinical failure defined as clinical, laboratory or radiographic findings suggestive of prosthetic joint infection at any time after reimplantation surgery.	model adjusted for propensity score, there was no significant difference in treatment failure rates between subjects treated with 6 weeks of antimicrobials and subjects treated with 4 weeks of antimicrobials HR= 1.4, 95% CI, 0.7-2.7; P= 0.31	Risk of bias: 4/8	between stages did not decrease the treatment failure rate in subjects with PJI compared with a weeks of treatment.  Study is about 2SR, not about DAIR or 1SR

Hsieh et al. 2009 [71]	Retrospective cohort study	Subjects: n=99 I: n=53	I: 1 week antibiotics	Free of infection - not defined in the article	Free of infection: 89 (90%)	SIGN quality of evidence: 2-	Conclusion: Short-term antibiotic therapy was
	Setting: single-centre, 2SR  Median follow- up time in months (range): 43 (24-60)	C: n=46  Type of PJI: 99 (100%) hip  Type of surgery: n=99 (100%) 2SR using an interim antibiotic-loaded cement spacer in the interim  Median age in years (range): I: 62 (28-76) C: 59 (22-81)  Male sex: n=60 (60.6%) I: n=33 (62.3%)	C: 4-6 weeks antibiotics	Persistent infection - defined as the presence of PHI after first-stage surgery.  Re-infection - PHI that occurred after the completion of SEA and antimicrobial therapy.  Medical costs  Hospital stay  Complications related to systemic antibiotic	I: n=47 (89%) C: n=42 (91%) P=0.67  Persistent infection: I: n=4 (8.5%) C: n=4 (9.5%) P= not stated  Re-infection I: n=3/50 (6.0%) C: n=2/44 (4.5%) P= not stated  Medical costs I: \$13732 C:\$21756 P=<0.001	Risk of bias: 4/8	not associated with a higher rate of treatment failure. Given the higher costs and incidence of complications, protracted courses of antibiotic administration may not necessarily be routine practice in subjects with PHI undergoing 2SR, provided that an antibiotic-loaded cement spacer is used.  Study is about 2SR, not about DAIR or 1SR
		C: n=27 (58.7%)  LTFU: 8 I: 3 C: 5		therapy	Hospital stay in days I: 18 C: 43 P=<0.001  Complications related to systemic antibiotic therapy I: 0 (0%) C: 5 (11%) P= not stated		

Lora-Tamayo et al. 2016 [95]	RCT  Setting: multicentre (17 centres)  Intention to treat analysis: Median follow- up time in days (IQR): 540 (not mentioned)	Intention to treat analysis Subjects: n=63 I: n=30 C: n=33  Type of PJI: I: 11 (37%) hip 19 (63%) knee C: 18 (55%) hip 15 (45%) knee  Type of surgery: n=63 (100%) DAIR  Median age in years (IQR): I: 70 (61–79) C: 74 (65–80)  Male sex: n=30 (48%) I: n=11 (37%) C: n=19 (58%)  LTFU: n=5 (8%) I: n=1 (2%) C: n=4 (6%)  Per protocol analysis Subjects: n=44 I: n=24 C: n=20	I: 8 weeks of levofloxacin plus rifampicin  C: 3 months or 6 months of levofloxacin plus rifampicin for hip and knee PJI respectively	Cure - defined as patients who retained the prosthesis, clinical signs of infection were resolved, and there had been a progressive decrease in C-reactive protein (CRP) levels.	Intention to treat analysis  Cure n=41 (65.1%) l: n=22 (73.3%) C: n=19 (57.6%) P = 0.190 Difference I and C groups (95% CI): - 15.7% (-39.2-7.3%)  Per protocol analysis  Cure n=41 (93.2%) l: n=22 (91.7%) C: n=19 (95.0%) Difference I and C groups (95% CI): 3.3% (-11.7-18.3%)	SIGN quality of evidence: 1- Risk of bias: 5/10	Conclusion: This is the first RCT suggesting that 8 weeks of levofloxacin plus rifampicin could be non-inferior to longer standard treatments for acute staphylococcal PJI managed with DAIR.  100% levofloxacin and rifampicin treatment  100% staphylococcal PJI

Ma et al. 2020 [122]	Retrospective cohort study  Setting: Single-centre, 2SR  Mean follow-up time in months (SD): 75.3 (30.6)	Subjects: n=64 I: n=21 C: n=43  Type of PJI: n=63 (100%) knee  Type of surgery: n=63 (100%) 2SR  Mean age in years (SD): 70.3 (11.0) I: 71.9 (8.2) C: 69.5 (12.2)  Male sex: n=21 (32.8%) I: n=3 (14.3%) C: n=18 (41.9%)  LTFU: not mentioned	I: <1 week of antibiotics  C: 4-6 weeks of antibiotics	Implant failure - defined as (1) recurrent delayed infection that required repeated resection arthroplasty, and (2) recurrent delayed infection that required chronic oral antibiotic suppression therapy.  Re-resection arthroplasty	Re-resection arthroplasty survival after 5 years I: 95.0% C: 75.8% - Kaplan-Meier survival analysis showed the survival rate of I group was not inferior to C group. P=0.08  Implant failure survival after 5 years I: 85.2% C: 74.0% - Kaplan-Meier survival analysis showed the survival rate of I group was not inferior to C group. P=0.317	SIGN quality of evidence:2- Risk of bias: 3/8	Conclusion: After the first stage of resection arthroplasty for a two-stage exchange arthroplasty, a short course of antibiotic treatment had similar implant survival rates in comparison to the standard 6-week course.  Study is about 2SR, not about DAIR or 1SR
		En o. not mentioned			group. 7 -0.317		

Puhto et al. 2011 Retrospective cohort study Setting: Setting: Single-centre Mean follow-up time in months (SD): 1: 26.2 (12) 1: 1: 28 1: 1: 28 1: 1: 28 1: 1: 28 1: 1: 28 1: 26.2 (12) 1: 1: 26.2 (12) 2: 1: 1: 28 2: 1: 26.2 (12) 3: 1: 1: 28 3: 1: 26.2 (12) 4: 1: 1: 28 5: 1: 26.2 (12) 5: 1: 1: 28 5: 1: 26.2 (12) 7: 1: 26.2 (12) 7: 1: 26.2 (12) 7: 1: 26.2 (12) 7: 1: 26.2 (12) 7: 1: 26.2 (12) 7:
C: 65 (9.9)  Male sex: n=21 (32.8%) I: n=21 (44%) C: n=18 (47%)

Spitzmuller et al. 2019 [105]	Case-control study  Setting: multicentre (3 academic referral institutions)  Follow-up time: 1 year	Subjects: n=269 Cases: n=59 Controls: n=210  Type of implant: Cases: n=28 (47%) total joint arthroplasty n=31 (53%) fracture fixation device Controls: n=157 (75%) total joint arthroplasty n=53 (25%) fracture fixation device  Type of surgery: any documented surgical procedure intended to cure the initial and reinfection (e.g., one- or two-stage revision with or without component retention or exchange, implant removal etc.) Numbers per type of surgery are not specified  Median age in years (IQR): Cases: 63 (48-71) Controls: 67 (55-73)	Case: subjects who sustained any reinfection demanding any surgical revision ≤1 year after the index procedure.  Controls: subjects who did not sustain any infection demanding surgical revision (or any surgical revision for infection) ≤1 year	Duration of antibiotic treatment	Univariate analysis: suggested an increased risk of recurrent infection with ≥14 days antibiotic treatment: OR (95% CI) 1.82 (1.00-3.28) P=0.049  Multivariate analysis: The odds of recurrence of implant-related infections was higher for subjects with antibiotic treatment lasting ≥14 days than for those with treatment shorter than 14 days: OR (95% CI) 1.85 (0.99-3.48), P=0.055, but this may be explained by bias due to start of suppressive therapy in this category.	SIGN quality of evidence: 2- Risk of bias:	NB: Focus is on fracture fixation devices not on PJI. Control status is fragile and might change to a case when subjects were followed up for a longer time-interval. Not controlled for type o surgery.  Conclusion: The optimal duration of systemic antibiotic treatment with surgical concepts of curing wound and device related orthopaedic infections is still unclear.

Male sex: Cases: 42 (71%) Controls: 106 (50%)

Yen et al. 2019 [99]	Systematic review and meta-analysis Included studies: 1 RCT and 9 observational studies	Subjects: n=856 I: 465 C: 580  Type of joints: knees, hips, shoulders, ankles or elbows.  Type of surgeries: DAIR, 2SR, 1SR  Range median/mean age: 61-77 years  Range proportion of men: 45-55%	I: short-course of antibiotics  C: long-course of antibiotics	Clinical event - defined as an event which included PJI-related death, re-infection and persistent infection	Clinical event I: 99 (21%) C: 141 (24%)  Meta-analysis showed no significant difference between short-course and long-course antibiotics: RR (95% CI) 0.87 (0.62– 1.22), P=0.051  The older the studied group was, the more short-course antibiotics were favoured.	SIGN quality of evidence: 2++ Risk of bias: 12/14	Conclusion: When treating PJI subjects following DAIR, an 8 week course of antibiotic therapy for total hip arthroplasty and a 75 day course for total knee arthroplasty may be a safe approach.  Antibiotics NB: Includes 4 studies that investigate the duration of solely intravenous antibiotics instead of the total time of oral or intravenous antibiotics.
Bernard et al. 2021 [102]	RCT Setting: multicentre (28 centres) Follow-up time: 2 years	Subjects: n= 410 I: n=205 C: n=205  LTFU: n=6  Type of PJI: n=255 (63.1%) hip	I: antibiotic therapy for 6 weeks C: antibiotic therapy for 12 weeks	Persistent infection within 2 years after the completion of antibiotic therapy - defined as the persistence or recurrence of infection with the initial	Intention to treat analysis: I: n=35 (18.1%) C: n=18 (9.4%) Risk difference (95% CI)=8.7 (1.8-15.6)	SIGN quality of evidence: 1+ Risk of bias: 8/10	Conclusion: Among patients with microbiologically confirmed prosthetic joint infections that were managed with standard surgical procedures, antibiotic therapy for 6

n=149 (36.9%) knee  Type of surgery: n=167 (41.3%) DAIR n=150 (37.1%) 1SR n=87 (21.5%) 2SR  Mean age in years (SD): I: 68.4 (11.7) C: 59.5 (10.7)  Male sex: n=273 (67.6%)	causative bacteria, with an antibiotic susceptibility pattern that was phenotypically indistinguishable from that at enrollment	Per protocol analysis: I: n=29 (17.6%) C: n=11 (6.9%) Risk difference (95% CI)=10.7 (3.6-17.9)	weeks was not shown to be noninferior to antibiotic therapy for 12 weeks and resulted in a higher percentage of patients with unfavorable outcomes.

Abbreviations: % = percentage;  $\ge$  = larger than or equal to; 1SR = one-stage revision; 2SR = two-stage revision; C = control group; CI = confidence interval; DAIR = debridement, antibiotics and implant retention; I = intervention group; IQR = interquartile range; LTFU = lost to follow-up; n = number; P = p-value; PJI = prosthetic joint infection; RCT = randomized controlled trial

Table 10 (Evidence for PICO 10, antibiotic holiday)

Reference	Study design, risk of bias, setting and follow up	Study population and characteristics	Intervention (I) and control (C) conditions	Outcome category	Results on primary and secondary outcomes + statistics	SIGN level of evidence	Comments
Ascione et	Study design	Patients (n):	I: Reimplantation	Cure	Outcome 1:	2+	Antibiotic treatment for 8
al. 2018	Prospective Cohort Study	I: n=82	with discontinuation		I: 65 (cure rate 79%)		weeks before reimplantation, (2 weeks iv, 6 weeks oral)
	Study	C: n=114	of antibiotic therapy of 2		C: 104 (cure rate 91%)		
	Risk of bias: 7/8	Mean age (years):	weeks (median 15 days, IQR 14- 17)		P=0.029		Cure rate higher in 46 immunocompromised patients in control group vs 31
	Cottings	I: 66 (57-75)					immunocompromised patients in intervention group (41/46 vs
	Setting:	C: 67 (58-74)	C:				20/31; X <sup>2</sup> =5.4, P=.02).
Inpa	Inpatient		Reimplantation without discontinuation				

	ollow up: 1edian 96 weeks	Male sex: I: 39 (47%) C: 52 (46%) Lost to follow up (n): I: 0 C: 0 Type of surgery: Two-stage revision	of antibiotic therapy				Cure rate in respect to continuous therapy not different in immunocompetent patients (63/68 vs 44/51; X²=1.3, P=.2)
2018 Ri Ci	ettrospective cohort Study  cisk of bias: 4/8  etting:  apatient, fulticentre  collow up:  -year	Patients (n):409 I: n=39/n=174 C: n=80  Lost to follow up (n): Unclear  Type of surgery: Two stage exchange arthroplasty	I: Reimplantation with an antibiotic holiday period of 1 week or 4 weeks  C: Reimplantation with an antibiotic holiday period of 2 weeks  I Holiday  C No Holiday	Treatment failure rate assessed using Delphi consensus criteria	Outcome 1: I: OR 1.45 P=.38/ OR 1.06 P=.83 C: OR 1.46 P=.23 I 146/174 = 84% no failure C 199/235 = 85% no failure	2-	The duration of antibiotic-free period and timing of reimplantation were at the surgeon's discretion  In the multivariate analysis, the duration of antibiotic-free period was not significantly associated with reinfection following reimplantation (OR, 0.93 per week; 95% CI, 0.81-1.06; P= .250)  Interim surgery before reimplantation (n=94): 41.5% on antibiotics, 58.5% during antibiotic holiday (P=.91)F

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