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

Guideline committee

E.J.G. Peters, MD, PhD (chair)	Department of Internal Medicine, Section of Infectious Diseases, Amsterdam University Medical Center; and, Amsterdam Institute for Infection and Immunity Institute, Infectious Diseases
S.A.V. van Asten, MD, PhD (coordinator)	Department of Medical Microbiology and infectious Diseases, Leiden University Medical Center
M. Wouthuyzen-Bakker, MD, PhD	Department of Medical Microbiology and Infection Prevention, University Medical Center Groningen
H. Scheper, MD, PhD (vice-chair)	Department of Infectious Diseases, Leiden University Medical Center
E.P.M. van Elzakker, MD	Department of Medical Microbiology and Infection Prevention, Amsterdam University Medical Center
L.L. Reubsaet, MD, PhD	Department of Medical Microbiology and Infection Prevention, Medical Center Haaglanden
M.W. Nijhof, MD, PhD	Department of Orthopedics, Sint Maartenskliniek, Nijmegen
H.C. Vogely, MD, PhD	Department of Orthopaedics, University Medical Center Groningen
Prof. P.C. Jutte, MD, PhD	Department of Orthopaedics, University Medical Center Groningen
P.D. van der Linden, PharmD, PhD	Department of Clinical Pharmacology, Tergooi Medical Center, (SWAB)
A. Plender, MD	Department of Internal Medicine, Amsterdam University Medical Center
G. van der Bij, MD, PhD	Department of Surgery, Spaarne Hospital

NVMM: Nederlandse Vereniging voor Medische Microbiologie (Dutch Society of Medical Microbiology); **NIV**: Nederlandse Internisten Vereniging (Dutch Society of Internal Medicine); **NVII**: Vereniging voor Infectieziekten (Dutch Society for Infectious Diseases); **NVIC**: Nederlandse Vereniging voor Intensive Care (Dutch Society for Intensive Care); **NVZA**: Nederlandse Vereniging van Ziekenhuisapothekers (Dutch Society of Hospital Pharmacists); **NVvAKI**: Nederlandse Vereniging voor Allergologie en Klinische Immunologie (Dutch Society for Allergology and Clinical Immunology); **NVK**: Nederlandse Vereniging voor Kindergeneeskunde (Dutch Society of Pediatrics); **NHG**: Nederlands Huisartsen Genootschap (Dutch College of General Practitioners); **NOV**: Nederlandse Orthopaedische Vereniging (Dutch Orthopaedic Association), **NvvH**: Nederlandse vereniging voor Heelkunde

Secretariaat SWAB p/a
Afdeling Infectieziekten, C5-P t.a.v. SWAB
Leids Universitair Medisch Centrum
Postbus 9600 2300 RC Leiden

Content

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. 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 (A-team) 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 2028 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[a]
DAIR for early acute PJI	vancomycin 40 mg/kg continuously /24 hr[b] (20 mg/kg loading dose) i.v. + ceftriaxone 2 g BID i.v. *or* vancomycin 40 mg/kg continuously /24 hr [b](20 mg/kg loading dose) i.v. + ceftazidime 6 g/ 24 i.v. (2 g loading dose need for *Pseudomonas* coverage according to local epidemiology)
DAIR for late acute hematogenous PJI	flucloxacillin 6 g/24 i.v. (loading dose 1g)[c] *or* flucloxacillin 6 g/24 i.v. (loading dose 1g)[c] + 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 40 mg/kg continuously /24 hr[b] (20 mg/kg loading dose
2SR after explantation / girdlestone[d]	Targeted therapy

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

[a] General remarks when starting empirical treatment for PJI:

- If a patient has a concomitant bacteremia, endocarditis or candidemia, empirical treatment may need to be adjusted according to the relevant SWAB guidelines.
- Dosing always needs to be adjusted to renal function
- 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.

[b] therapeutic drug monitoring (TDM) serum vancomycin through concentration in intermittent infusion > 15 mg/L, steady state concentration for continuous infusion 17-25 mg/L.

[c] Flucloxacillin range 6-12 g/ 24 hours (in case of 12 g/24 hr, loading dose 2 g)

[d] 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 1SR			
Methicillin-sensitive staphylococci	flucloxacillin 6 g/24h[b] 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[e] po)	rifampicin 450 mg BID + clindamycin 600 mg TID *or* rifampicin 450 mg BID + trimethoprim-sulfamethoxazole 960 mg BID[c] † *or* clindamycin 600mg TID *or* rifampicin 450 mg BID + minocyclin 100 mg BD (loading dose 200mg)	cefazolin 4-6 g/24h i.v.[d] (after loading dose of 1 gram for 1-2 weeks instead of flucloxacillin
Methicillin-resistent staphylococci	vancomycin 40 mg/kg continuously /24 hr (20 mg/kg loading dose) OR 1000 mg TID[a] 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[e] po†)	rifampicin 450 mg BID + clindamycin 600 mg TID *or* rifampicin 450 mg BID + trimethoprim-sulfamethoxazole 960 mg BID[c] *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[e] p.o.	trimethoprim-sulfamethoxazole 960 mg BID p.o.[c]	
P. aeruginosa	ceftazidime 6 g/24hours i.v. (after loading		

	dose 2 g) for 1-2 weeks *followed by* ciprofloxacin 750 mg BID[e] p.o.		
C. acnes	penicillin G 6MU/24h[f] 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.		ceftriaxone 2 g 1dd i.v. † *followed by* clindamycin 600 mg TID p.o.
Streptococci	penicillin G 6MU † /24h[f] 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/24h[g] 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[i]	vancomycin 40 mg/kg continuously /24 hr (20 mg/kg loading dose) OR 1000 mg TID for 1-2 weeks *followed by* linezolid 600 mg BID p.o. or continuous vancomycin iv therapy)
Enterococci - Amoxicillin resistant	vancomycin 40 mg/kg continuously /24 hr (20 mg/kg loading dose) OR 1000 mg TID [a] for 2 weeks followed by linezolid 600 mg BID[i]	linezolid 600 mg p.o. BID[i]	
Anaerobes	dependent on antibiogram: penicillin G 6MU/24h[f] 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)^ *or* amoxicillin-clavulanic acid 4dd 1200 mg i.v. for 1 -2 weeks, *followed by* amoxicillin-clavulanic acid 3dd 875/125 mg p.o.		
Candida (2 stage revision arthroplasty preferable) - fluconazole susceptible	fluconazole 400 mg[h] OD (loading dose 800 mg)		

Candida (2 stage revision arthroplasty preferable) - fluconazole resistant	voriconazole 2dd 200 mg[h] p.o. (after loading dose of 2dd 400 mg p.o.) if susceptible *or* 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.[b] † (after loading dose 1 gram) for 1-2 weeks followed by: clindamycin 600 mg TID	trimethoprim-sulfamethoxazole 960mg BID † *or* flucloxacillin 1000mg 5 times daily p.o. (only if adequate absorption test)	cefazolin 6 g/24h i.v. † (after loading dose 1 gram) for 1-2 weeks followed by: clindamycin 600 mg TID
Methicillin-resistent staphylococci	vancomycin 40 mg/kg continuously /24 hr i.v. (20 mg/kg loading dose) OR 1000 mg TID[a] 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[g] IV for 2 weeks, † after loading dose of 1 g. *followed by* amoxicillin 750 mg TID p.o.	linezolid 600 mg p.o. BID[i] maximum duration of 6 weeks#	vancomycin 40 mg/kg continuously /24 hr (20 mg/kg loading dose)
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		
Chronic antibiotic suppressive treatment (starts after 6 weeks of antibiotic treatment 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[h] OD		
All other organisms	discuss in multidisciplinary team		
Arthrodesis or amputation			
Start targeted therapy conform 2SR but with altered duration: - In case of complete resection of infected bone: stop antibiotics after 48 hours - in case of partial resection of infected bone continue antibiotics for a minimum of 6 weeks			

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

[a] therapeutic drug monitoring (TDM) weekly kidney function and serum vancomycin trough concentration in intermittent infusion > 15 mg/L, steady state concentration for continuous infusion 17-25 mg/L.

[b] Flucloxacillin dose range 6-12 g/24 hr (in case of 12 g/24, loading dose 2 g)

[c] Trimethoprim-sulfamethoxazole (co-trimoxazole) dose range 960 mg BID - 960 mg TID

[d] Cefazolin range 4-6g/24 hr, based on www.eucast.org/fileadmin/src/media/PDFs/EUCAST_files/Guidance_documents/Cefotaxime_and_Ceftriaxone_for_Staphylococcus_aureus_Infections_-_January_2023.pdf

[e] 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

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

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

[h] Fluconazol, voriconazole: check levels in blood for potential dosage adjustments

[i] 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 multi-resistant 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.

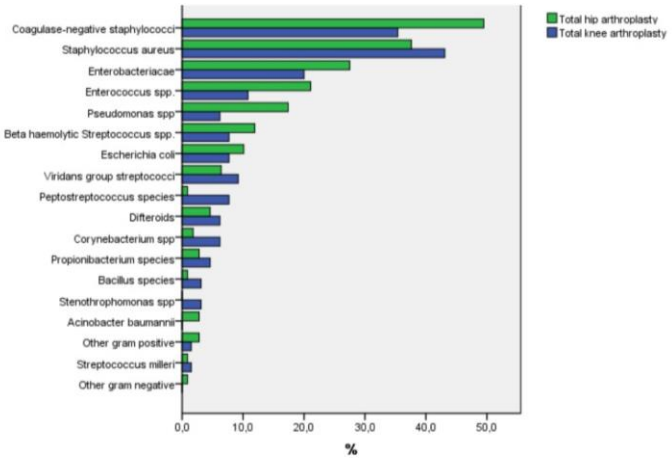

Figure 1: microorganisms associated with PJI in total hip and total knee arthroplasties.
Copied from de Vries et al.[28]

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 co-drug 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 β-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 β-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 coagulase-negative 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 gram-negative 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 pre-clinical 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 α-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; X^2=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 "peri-prosthetic"[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 ("Staphylococcus"[Mesh] OR "staphylococci"[tw] OR "S. aureus"[tw] OR "Staphylococcus"[tw] OR "Staphylococcal"[tw] OR "Cons"[tiab])

Hits per database:
- Pubmed: 1583
- Embase: 3185
- Coch/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 amoxicillin
C oral treatment with clindamycin
O cure

Search string: ("PJI"[tiab] OR (("Prostheses and Implants"[Mesh] OR "periprosthetic"[tw] OR "peri-prosthetic"[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 ("Streptococcus"[Mesh] OR "streptococcus"[tw] OR "streptococci"[tw] OR "streptococcal"[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 "peri-prosthetic"[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 ("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 "peri-prosthetic"[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 ("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 amoxicillin
C oral treatment with clindamycin
O cure

PICO ab:
P *C. acnes* PJI
I rifampicin-based antibiotic regimen
C non-rifampicin-based antibiotic regimen
O cure

Search string: ("PJI"[tiab] OR (("Prostheses and Implants"[Mesh] OR "periprosthetic"[tw] OR "peri-prosthetic"[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 **("**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 "peri-prosthetic"[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 ("Candida"[mesh] OR "Candida"[tw] OR "Candidas"[tw])

Hits per database:
Hits Pubmed: 121
Hits Embase: 275

Culture-negative

PICO 7:
P: Culture-negative PJI

I: fluoroquinolone combined with rifampicin
C: other antibiotic regimen
O: Cure

Search string: ("PJI"[tiab] OR (("Prostheses and Implants"[Mesh] OR "periprosthetic"[tw] OR "peri-prosthetic"[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:
P Suppressive AB for incurable PJI
I <2y of suppressive AB
C >2y of suppressive AB
O Need for surgical reintervention

Search string: ("PJI"[tiab] OR (("Prostheses and Implants"[Mesh] OR "periprosthetic"[tw] OR "peri-prosthetic"[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
O: Cure

PICO 9b:
P: Chronic PJIs treated with one-stage revision surgery
I: 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 "peri-prosthetic"[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 antibiotic
C: Reimplantation without antibiotic holiday/withholding of antibiotic
O: Cure

Search string: ("PJI"[tiab] OR (("Prostheses and Implants"[Mesh] OR "periprosthetic"[tw] OR "peri-prosthetic"[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 ("two-stage"[tw] OR "two stage"[tw] OR "two-stages"[tw] OR "two stages"[tw] OR "2 stage"[tw] OR "2-stage"[tw] OR "2 stages"[tw] OR "2-stages"[tw]) AND ("surgical procedures, operative"[mesh] OR "Arthroplasty"[Mesh] OR arthroplasty[tw]) AND (holiday[tw] OR withhold*[tw] OR "Withholding Treatment"[Mesh])

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 "peri-prosthetic"[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 ("timing"[tw] OR "immediate"[tw] OR "immediately"[tw] OR "delay"[tw] OR "delaying"[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 "Staphylococcal"[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	Intervention clearly defined	Outcome clearly defined	Outcome assessed blind for exposure	Withdrawal/ drop-out acceptable (<20%)	Selective loss to follow-up excluded	Major confounders/ 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

Reference		**Aydin et al. 2021 [43]**
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?	+
1.10	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.	+
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 the included randomized controlled trial for PICO 1a and 1b

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	Intervention clearly defined	Outcome clearly defined	Outcome assessed blind for exposure	Withdrawal/ drop-out acceptable (<20%)	Selective loss to follow-up excluded	Major confounders/ 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

Reference		**Aydin et al. 2021 [43]**
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?	+
1.10	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.	+
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	Intervention clearly defined	Outcome clearly defined	Outcome assessed blind for exposure	Withdrawal/ drop-out acceptable (<20%)	Selective loss to follow-up excluded	Major confounders/ 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	Intervention clearly defined	Outcome clearly defined	Outcome assessed blind for exposure	Withdrawal/ drop-out acceptable (<20%)	Selective loss to follow-up excluded	Major confounders/ 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	Intervention clearly defined	Outcome clearly defined	Outcome assessed blind for exposure	Withdrawal/ drop-out acceptable (<20%)	Selective loss to follow-up excluded	Major confounders/ 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

Reference		**Aydin et al. 2021 [43]**
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?	+
1.10	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.	+
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 6: Risk of bias of included publications for PICO 6

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

Commented [1]: niet de juiste tabellen gebruikt voor literature review

Commented [2]: niet de juiste tabellen gebruikt voor literature review

Commented [3]: niet de juiste tabellen gebruikt voor literature review

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

Reference		**Yoon et al. 2017 [85]**	**Reisener & Perka 2018 [88]**
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?	-	+/-
1.10	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.	+	+
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**: 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	Intervention clearly defined	Outcome clearly defined	Outcome assessed blind for exposure	Withdrawal/ drop-out acceptable (<20%)	Selective loss to follow-up excluded	Major confounders/ 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?	+
1.10	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.	+
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**: This article does not assess PICO-question	

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

Reference	Study groups defined	Selection bias avoided/ excluded	Intervention clearly defined	Outcome clearly defined	Outcome assessed blind for exposure	Withdrawal/ drop-out acceptable (<20%)	Selective loss to follow-up excluded	Major confounders/ prognostic factors identified and controlled	Score

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

Reference		**Yen et al. 2019 [99]**
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?	+
1.10	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.	+

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]
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?	+	+	+

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

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

Becker et al. 2020 [36]	Retrospective multicentre cohort study Setting: Inpatient Follow up: All 79 subjects/pathogens: 435 days (IQR 107.5, 834)	subjects (n): All subjects/pathogens: 79 I: n=58 (SA and CNS) C: n=21 (SA and CNS) Mean age (years): All subjects/pathogens: 71 [63.5, 81] years I: n.r C: n.r. Male sex: All subjects/pathogens: 70% I: n.r. C: n.r. Lost to follow up (n): I: 0 C: 0 Type of surgery: DAIR hip knee	I: Rifampicin C: No rifampicin	In remission vs failure	Outcome 1: (both SA and CNS) I: 41 (cure rate 75.9%) C: 13 (cure rate 62%) P=0.64 (S aureus/CNS not specified)	SIGN quality of evidence: 2- Risk of bias: 3/8	65 SA, 16 CNS (incl 2 both) Rifampicin use 41x (75.9%) success, 17x (68%) failure p=0.64, Hazard ratio univariate Cox 0.17[0.06, 0.45] p<0.001, multivariate Cox Inf[0.00, Inf] p=0.998 (NS) Rifampicin + fluoroquinolone 31 (57.4%) success, 5 (20%) failure p=0.004 Hazard ratio univariate Cox 0.19[0.07, 0.53] p=0.002, multivariate Cox 0.28[0.02, 3.83] p=0.338 (NS) Duration of rifampicin (days) Hazard ratio multivariate Cox 0.95[0.92, 0.99] p=0.022.

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

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

Lora-Tamayo et al. 2013 [40]	Study design retrospective, multicentre, observational study Setting: Inpatient Follow up: Not specified (>28 months)	subjects (n):total 345 I: n=303 rifa C: n=42 (?) Mean age (years): All subjects 73 (27-95) I: n.r. C: n.r. Male sex: All subjects: 41% I: n.r. C: n.r. Lost to follow up (n): Total 17 (5%) (volgens Kaplan Meier 174 (54%)? I: 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: 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	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

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) I: 68 (cure rate 87 %) C: 11 (cure rate 100%) No relapse I: 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.

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

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

Lora-Tamayo et al. 2017 [55]	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 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 Setting: inpatient Follow up:>2years	subjects (n): 70 I: n=31 C: n=39 Mean age (years):77 (69-83) I: not stated C: not stated Male sex:38 (54%) I: not stated C: not stated Lost to follow up (n): not stated Type of surgery:	I: Rifampicin C: No rifampicin	Failure: A new sample from which the same Streptococcus spp was isolated as was identified in the previous infected joint prosthesis was defined as relapse of the infection. Isolation of another microorganism was considered as reinfection.	Outcome: failure I: 8 C: 11 RR 1.08 (0.41 – 2.89)	SIGN quality of evidence: 2- Risk of bias: 3/8	No evaluation of survivor or selection bias. (3x quitting rifampicin needed:1x hepatitis, 1x thrombocytopenia, 1x severe diarrhoea)

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

Table 3: Evidence Table for PICO 3 (Enterococci)

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

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 re-appeared 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 I: 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 Follow up: Minimum of 1 year.	subjects (n): 49 I: 8 C: 41 Lost to follow up (n): 0 Type of surgery: DAIR, revision surgery, no surgery.	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. Failure: chronic antimicrobial suppression therapy, permanent removal of implant, amputation, relapse or death from the infection. Re-infection with new pathogens was not considered as failure, and neither repeated surgical debridement to control the infection.	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)

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.

El Helou et al. 2008 [60]	Retrospective cohort study Setting: single-centre Median follow up in days (range): 1253 (29-4610)	Episodes: n=50 (in n=47 subjects) I: n=19 C: n=31 Median age in years (range): 70 (32-89) Male sex: n=25 (50%) TKP: n=24 (48%) THP: n=26 (52%) Type of surgery: n=17 (34%) 2SR n=4 (8%) 1SR n=5 (10%) DAIR n=1 (2%) amputation n=23 (46%) resection arthroplasty	I: Combination therapy C: Monotherapy	Treatment failure - defined as one of the following criteria: recurrence of PJI due to the same enterococcal strain or a different microorganism; acute inflammation on histopathological examination; development of a sinus tract communicating with the prosthesis at any time after surgery; death due to prosthesis-related infection; or indeterminate clinical failure, defined as clinical, laboratory, or radiological findings suggestive of PJI at any time after surgical therapy. Cranial nerve VIII toxicity Nephrotoxicity	Treatment failure I: n=7 (37%) C: n=5 (16%) P=0.2 Cranial nerve VIII toxicity I: n=6 (32%) C: n=0 (0%) P=0.002 Nephrotoxicity I: n=5 (26%) C: n=2 (6%) P=0.09	SIGN quality of evidence: 2- Risk of bias:4/8	Additive agents for combination therapy: aminoglycoside

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 trimethoprim-sulfamethoxazole.

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

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 Male sex: I: not stated C: not stated LTFU: 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. <u>Conclusion</u>: In the *C acnes* subsets, neither individual nor combined analysis favoured rifampicin-based regimens. <u>Rifampicin doses:</u> not mentioned. <u>Side-effects of rifampicin:</u> not mentioned <u>Antibiotic combinations:</u> not mentioned.

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

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=4 (3.8%) Explantation without new prosthesis	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 *C acnes*. 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).

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

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

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

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. <u>IIV Antibiotics in intervention group:</u> (all during 6 weeks) > n=44 subjects: vancomycin and cefepime. > n=2 (4.3%) monotherapy vancomycin

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

Huang et al. 2012 [90]	Retrospective cohort study Setting: single-centre Mean follow-up time in months (range): I: 47 (12-119) C: 33.2 (12-125.7)	Subjects: n=343 I in 298 subjects I: n=48 I/subjects C: n=295 I in 250 subjects Type of PJI: I: - n=21 hip (38%) - n=28 knee (51%) C: Not mentioned Mean age in years (range): I: 63.7 (39-85) C: 66.7 (18-89) Male sex: I: 19 (40%) C: 122 (49%) Lost to follow up: n=25 Type of initial surgery: I: n=12 (25%) I&D n=33 (69%) 2SR n=3 (6%) 1SR 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	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 to infection.	Infection control I: n=37 (73%) C: 73% *P*=1.00 Survival Kaplan Meier shows similar infection-free survival between I and C after I&D (*P*=0.73) and 2SE (*P*=0.96) n=11 (28.2%) of I who were treated with vancomycin failed treatment.	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-sensitive gram-positive organisms may still be the most common culprit in culture-negative infections. <u>IV Antibiotics in intervention group:</u> n=39 minimum of 4 weeks vancomycin iv > sometimes combined with ciprofloxacin iv (n=2), ciprofloxacin po (n=4), doxycycline iv (n=1), rifampicin po (n=1), ceftriaxone iv (n=1), vancomycin po (n=1) n=4 ceftriaxone n=1 ceftazidime n=1 daptomycin and oral ciprofloxacin n=1 nafcillin iv n=1 no antibiotics

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

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

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. <u>IV Antibiotics in intervention group:</u> 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 cox-regression 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. <u>IV Antibiotics in intervention group:</u> I: rifampicin and levofloxacin.

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

Abbreviations: % = percentage; ≥ = 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; n = number; *P* = p-value; PJI = prosthetic joint infection

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

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

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=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%) LTFU: n=<21	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%)

Leijtens et al. 2019 [114]	Retrospective case series Setting: single-centre Median follow-up in months: 33	Subjects: n=23 Mean age in years (range): 70 (40-88) Type of PJI: n=21 (91.3%) total hip arthroplasty n=2 (8.7%) hemiarthroplasty Type of surgery: n=13 (56.5%) DAIR n=7 (30.4%) partial or total revision n=3 (12.5%) non-surgical Male sex: 7 (30.4%) Mean age in years (SD): Cases: 74.3 (13.9) Controls: 76.3 (13.9)	N/A	SAT successful - cases with retention of the prosthesis without clinical relapse of infection at final follow-up. Failure - was defined as death related to PJI or new surgical intervention at prosthesis side due to persistent or recurrent infection.	The mean duration of SAT in months (range): 38 (1-151) SAT successful: n=13 (56.5%)	SIGN quality of evidence: 3 Risk of bias:

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

Pradier et al. 2018 [116]	Retrospective case series Setting: single-centre Mean follow-up in days (SD): 1020 (597)	Subjects: n=78 Type of PJI: n=35 (45%) hip 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): 64.1 (16.8)	N/A	Remission - defined as the absence of signs of infection assessed at least 24 months after 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. Adverse events likely attributable to SAT SAT discontinuation	Failure: n=22 (28.3%) Adverse events likely attributable to SAT: n=14 (18%) SAT discontinuation: n=6 (8%)	SIGN quality of evidence: 3 Risk of bias:	Aim: to describe the use of oral tetracyclines as SAT in subjects with PJI

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 Median age in years (IQR): 83 (81-88) Male sex: 64 (47.1%)	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%) Survival rate without an event after 2 years (95% CI): 61% (51-74)	SIGN quality of evidence: 3 Risk of bias:	Subjects >= 75 years

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

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.

Sandiford et al. 2020 [119]	Retrospective case series Setting: single centre Mean follow-up in years (range): 3.2 (1.3–5.7).	Subjects: n=26 Type of PJI: n=10 (38%) hip n= 16 (62%) knee Type of surgery: n=4 (15%) 1SR n=4 (15%) 2SR n=15 (58%)DAIR n=3 (12%) none Mean age in years (range): 72 (35-93) LTFU: n=2/26 Mean duration of SAT in years: 3.1	N/A	Success rate- defined as no admissions due to sepsis arising from the affected joint; no progression to further surgery or death from related causes. Adverse reaction to the antibiotics used	Success rate: n=20 (83%) Adverse reaction to the antibiotics used n=2	SIGN quality of evidence: 3 Risk of bias:	Conclusion: Prolonged suppressive antibiotic therapy is a viable option for the management of PJI with a low incidence of complications.

Wouthuyzen-Bakker et al. 2017 [120]	Retrospective case series Setting: Single centre Median follow-up in months (range): 21 (3-81)	Subjects: n=21 Type of PJI: n=13 (62%) hip n=6 (29%) knee n=2 (10%) shoulder Type of surgery: n=3 (14%) DAIR n=8 (38%) lavage n=3 (14%) DAIR + lavage n=1 (5%) reposition n=1 (5%) excision 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	N/A	Failure - defined as subjects who still experienced joint pain, when surgical intervention (debridement, removal, arthrodesis or amputation) was needed to control the infection and/or when death occurred due to the infection.	Failure: n=7 (33%) Treatment success: Standard prosthesis: 90% Tumor prosthesis: 50% Side-effects of antibiotics: 43%	SIGN quality of evidence: 3 Risk of bias:

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

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 New infection	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:	<u>Conclusion:</u> a six-week course of antibiotics in knee and hip PJIs treated with 1SR has a satisfactory remission rate in this open study.

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 LTFU: 0 (0%)	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. Controls: subjects without 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:	<u>Conclusion:</u> Chronic antibiotic suppression should be considered following THA I&D with head and liner exchange.

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: <u>NB: NOT ONLY PJI</u> 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%) <u>Intention to treat analysis:</u> LTFU: 0 (0%) <u>Per protocol analysis:</u> LTFU: 6 (4.9%) I: 3 (4.8%) C: 3 (4.9%)	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 .	<u>Intention to treat analysis:</u> 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 <u>Per protocol analysis:</u> Remission I: 57 (95%) C: 54 (95%) *P*=0.95 Significant antibiotic-related adverse events I: 17 (28%) C: 19 (33%) *P*= 0.56	SIGN quality of evidence:1+ Risk of bias: 8/10	**<u>NB: not only PJI</u>** <u>Conclusion:</u> 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)

Bernard et al. 2010 [98]	Prospective cohort study Setting: single-centre Median follow-up time in months (range): 36 (26-65)	Subjects n=144 I: n=70 C: n=74 Type of PJI: - n=62 (43%) hip arthroplasties - n=62 (43%) knee arthroplasties - n=20 (14%) hip hemiarthroplasties Type of surgery: I: - n=20 (29%) DAIR - n=4 (6%) 1SR - n=36 (51%) 2SR - n=24 (35%) none C: - n=40 (54%) DAIR - n=6 (8%) 1SR - n=20 (27%) 2SR - n=27 (37%) none Median age in years (IQR): 77 (67-82) Male sex: n=69 (47.9%) I: n=32 (45.7%) C: n=37 (50.0%) LTFU: not stated	I: 6 weeks antibiotics C: 12 weeks antibiotics	Cure – defined as the absence of clinical, radiological and biological signs of infection in the area of the arthroplasty after a minimum follow-up of 24 months post-surgery.	Cure: n=115 (80%) I: n=63 (90%) C: n=61 (68.9%) *P*= not stated Overall logistic regression in multivariate analysis: six weeks' antibiotic treatment: OR 2.7 (0.96-7.8). Significant interaction with variables "2SE" and "implant removed".	SIGN quality of evidence: 1+ Risk of bias: 5/8	Conclusion: following surgery for treatment of PJI, antibiotic therapy might be able to be limited to a 6-week course, with only a few days of intravenous administration. This approach needs confirmation in RCT's.

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

El Helou et al. 2011 [123]	Retrospective cohort study Setting: single-centre, 2SR Mean follow-up time in years (SD): I: 6.6 (10.3) C: 4.5 (2.8)	Subjects: n=208 I: n=82 C: n=126 Type of PJI: I: n=36 (43.9%) hip n=46 (56.1%) knee C: n=63 (50.0%) hip n=63 (50.0%) knee Type of surgery: n=208 (100%) 2SR Mean age in years (SD): I: 67.2 (9.8) C: 67.8 (10.4) Male sex: n=109 (52.4%) I: n=48 (58.5%) C: n=61 (51.6%) LTFU: not mentioned	I: 4 weeks iv antibiotics C: 6 weeks iv antibiotics	Treatment failure - defined by one of the 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.	From the Cox Proportional Hazards 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	SIGN quality of evidence: 2- Risk of bias: 4/8	Conclusion: Six weeks of parenteral antimicrobials between stages did not decrease the treatment failure rate in subjects with PJI compared with 4 weeks of treatment. Study is about 2SR, not about DAIR or 1SR

Hsieh et al. 2009 [71]	Retrospective cohort study Setting: single-centre, 2SR Median follow-up time in months (range): 43 (24-60)	Subjects: n=99 I: n=53 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: n=27 (58.7%) LTFU: 8 I: 3 C: 5	I: 1 week antibiotics C: 4-6 weeks antibiotics	Free of infection - not defined in the article 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 therapy	Free of infection: 89 (90%) 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 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	SIGN quality of evidence: 2- Risk of bias: 4/8	<u>Conclusion</u>: Short-term antibiotic therapy was 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

Lora-Tamayo et al. 2016 [95]	RCT Setting: multicentre (17 centres) <u>Intention to treat analysis:</u> Median follow-up time in days (IQR): 540 (not mentioned)	<u>Intention to treat analysis</u> 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%) <u>Per protocol analysis</u> 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.	<u>Intention to treat analysis</u> Cure n=41 (65.1%) I: 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%) <u>Per protocol analysis</u> Cure n=41 (93.2%) I: 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	<u>Conclusion</u>: 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 arthro-plasty 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

Puhto et al. 2011	Retrospective cohort study Setting: Single-centre Mean follow-up time in months (SD): I: 26.2 (12) C: 50.6 (29)	<u>Intention to treat analysis:</u> Subjects: n=132 I: n=72 C: n=60 LTFU: 4 <u>Per protocol analysis:</u> Subjects: n=86 I: n=48 C: n=38 Type of PJI: n=32 (37%) hip n=54 (63%) knee Type of surgery: n=86 (100%) DAIR Mean age in years (SD): I: 70 (10.4) C: 65 (9.9) Male sex: n=21 (32.8%) I: n=21 (44%) C: n=18 (47%)	I: 3 or 2 months of antibiotics for hip and knee PJI respectively C: 6 or 3 months months of antibiotics for hip and knee PJI respectively	Treatment success - defined as achieved when the original prosthesis was retained and the patient had no symptoms or signs of infection and C-reactive protein and sedimentation rate were normal at the end of follow-up.	<u>Intention to treat analysis:</u> Treatment success I: 42 (58.3%) C: 34 (56.7%) p=0.85 <u>Per protocol analysis:</u> Treatment success I: n=42 (87.5%) C: n=34 (89.5%) *P*=0.78	SIGN quality of evidence:2- Risk of bias: 4/8	<u>Conclusion</u>: if the subject completes the antibiotic therapy, treatment duration of 3 months in TKA PJIs and 2 months in THA PJIs is as good as longer antibiotic treatment of 6 months or 3 months, respectively, in subjects treated with DAIR.

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) Male sex: Cases: 42 (71%) Controls: 106 (50%)	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 of surgery. Conclusion: The optimal duration of systemic antibiotic treatment with surgical concepts of curing wound and device-related orthopaedic infections is still unclear.

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	<u>Conclusion</u>: 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. <u>Antibiotics</u> 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: multi-centre (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	<u>Intention to treat analysis:</u> 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	<u>Conclusion</u>: 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	<u>Per protocol analysis:</u> 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; ≥ = 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 al. 2018	Study design Prospective Cohort Study Risk of bias: 7/8 Setting: Inpatient	Patients (n): I: n=82 C: n=114 Mean age (years): I: 66 (57-75) C: 67 (58-74)	I: Reimplantation with discontinuation of antibiotic therapy of 2 weeks (median 15 days, IQR 14-17) C: Reimplantation without discontinuation	Cure	Outcome 1: I: 65 (cure rate 79%) C: 104 (cure rate 91%) P=0.029	2+	Antibiotic treatment for 8 weeks before reimplantation, (2 weeks iv, 6 weeks oral) Cure rate higher in 46 immunocompromised patients in control group vs 31 immunocompromised patients in intervention group (41/46 vs 20/31; X^2=5.4, P=.02).

	Follow up: Median 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; X^2=1.3, P=.2)
Tan et al. 2018	Study design Retrospective Cohort Study Risk of bias: 4/8 Setting: Inpatient, Multicentre Follow up: 1-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

References

1. Dutch Arthroplasty Register. LROI. Annual report 2022. Available at: https://www.lroi-report.nl. Accessed June 10.
2. Tande AJ, Patel R. Prosthetic joint infection. Clin Microbiol Rev **2014**; 27(2): 302-45.
3. Osmon DR, Berbari EF, Berendt AR, et al. Diagnosis and management of prosthetic joint infection: clinical practice guidelines by the Infectious Diseases Society of America. Clin Infect Dis **2013**; 56(1): e1-e25.
4. Ariza J, Cobo J, Baraia-Etxaburu J, et al. Executive summary of management of prosthetic joint infections. Clinical practice guidelines by the Spanish Society of Infectious Diseases and Clinical Microbiology (SEIMC). Enfermedades Infecciosas y Microbiologia Clinica **2017**; 35(3): 189-95.
5. Parvizi J, Gehrke T, Mont MA, Callaghan JJ. Introduction: Proceedings of International Consensus on Orthopedic Infections. J Arthroplasty **2019**; 34(2S): S1-S2.
6. Nederlandse Orthopaedische Vereniging (NOV). Aanbeveling Werkwijze behandeling Prothese Infecties Orthopedie. Available at: https://www.orthopeden.org/media/tjdlhrcv/aanbeveling-werkwijze-behandeling-prothese-infecties-orthopedie.pdf. Accessed June 9.
7. Parvizi J, Gehrke T, Chen AF. Proceedings of the International Consensus on Periprosthetic Joint Infection. Bone Joint J **2013**; 95-B(11): 1450-2.
8. Signore A, Sconfienza LM, Borens O, et al. Consensus document for the diagnosis of prosthetic joint infections: a joint paper by the EANM, EBJIS, and ESR (with ESCMID endorsement). Eur J Nucl Med Mol Imaging **2019**; 46(4): 971-88.
9. Brouwers MC, Kho ME, Browman GP, et al. AGREE II: advancing guideline development, reporting and evaluation in health care. Can Med Assoc J **2010**; 182(18): E839-E42.
10. Pappas PG, Kauffman CA, Andes DR, et al. Clinical Practice Guideline for the Management of Candidiasis: 2016 Update by the Infectious Diseases Society of America. Clin Infect Dis **2016**; 62(4): e1-50.
11. Guyatt GH, Oxman AD, Vist GE, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. BMJ (Clinical research ed) **2008**; 336(7650): 924-6.
12. Alonso-Coello P, Oxman AD, Moberg J, et al. GRADE Evidence to Decision (EtD) frameworks: a systematic and transparent approach to making well informed healthcare choices. 2: Clinical practice guidelines. BMJ (Clinical research ed) **2016**; 353: i2089.
13. Stichting Werkgroep Antibioticabeleid (SWAB). The Dutch Working Party on Antibiotic Policy (SWAB) guideline for the approach to suspected Antibiotic Allergy. Available at: https://swab.nl/exec/file/download/192. Accessed June 9.
14. Atkins BL, Athanasou N, Deeks JJ, et al. Prospective evaluation of criteria for microbiological diagnosis of prosthetic-joint infection at revision arthroplasty. The OSIRIS Collaborative Study Group. Journal of clinical microbiology **1998**; 36(10): 2932-9.
15. Trampuz A, Piper KE, Jacobson MJ, et al. Sonication of removed hip and knee prostheses for diagnosis of infection. The New England journal of medicine **2007**; 357(7): 654-63.
16. Oethinger M, Warner DK, Schindler SA, Kobayashi H, Bauer TW. Diagnosing periprosthetic infection: false-positive intraoperative Gram stains. Clin Orthop Relat Res **2011**; 469(4): 954-60.
17. Osmon DR, Hanssen AD, Patel R. Prosthetic joint infection: Criteria for future definitions. Clinical Orthopaedics and Related Research **2005**; (437): 89-90.
18. Peel TN, Spelman T, Dylla BL, et al. Optimal Periprosthetic Tissue Specimen Number for Diagnosis of Prosthetic Joint Infection. Journal of clinical microbiology **2017**; 55(1): 234-43.
19. Li HK, Rombach I, Zambellas R, et al. Oral versus Intravenous Antibiotics for Bone and Joint Infection. The New England journal of medicine **2019**; 380(5): 425-36.
20. Wald-Dickler N, Holtom PD, Phillips MC, et al. Oral Is the New IV. Challenging Decades of Blood and Bone Infection Dogma: A Systematic Review. The American journal of medicine **2022**; 135(3): 369-79 e1.
21. Bocle H, Lavigne JP, Cellier N, et al. Effectiveness of early switching from intravenous to oral antibiotic therapy in Staphylococcus aureus prosthetic bone and joint or orthopedic metalware-associated infections. BMC Musculoskelet Disord **2021**; 22(1): 315.
22. Wagenaar FBM, Lowik CAM, Zahar A, Jutte PC, Gehrke T, Parvizi J. Persistent Wound Drainage After Total Joint Arthroplasty: A Narrative Review. J Arthroplasty **2019**; 34(1): 175-82.

23. Byren I, Bejon P, Atkins BL, et al. One hundred and twelve infected arthroplasties treated with 'DAIR' (debridement, antibiotics and implant retention): antibiotic duration and outcome. The Journal of antimicrobial chemotherapy **2009**; 63(6): 1264-71.
24. Arciola CR, An YH, Campoccia D, Donati ME, Montanaro L. Etiology of implant orthopedic infections: A survey on 1027 clinical isolates. International Journal of Artificial Organs **2005**; 28(11): 1091-100.
25. Sousa R, Pereira A, Massada M, da Silva MV, Lemos R, Costa e Castro J. Empirical antibiotic therapy in prosthetic joint infections. Acta Orthop Belg **2010**; 76(2): 254-9.
26. Moran E, Masters S, Berendt AR, McLardy-Smith P, Byren I, Atkins BL. Guiding empirical antibiotic therapy in orthopaedics: The microbiology of prosthetic joint infection managed by debridement, irrigation and prosthesis retention. The Journal of infection **2007**; 55(1): 1-7.
27. Van Erp JHJ, Heineken AC, Van Wensen RJA, et al. Optimization of the empirical antibiotic choice during the treatment of acute prosthetic joint infections: a retrospective analysis of 91 patients. Acta Orthop **2019**; 90(5): 455-9.
28. de Vries L, van der Weegen W, Neve WC, Das H, Ridwan BU, Steens J. The Effectiveness of Debridement, Antibiotics and Irrigation for Periprosthetic Joint Infections after Primary Hip and Knee Arthroplasty. A 15 Years Retrospective Study in Two Community Hospitals in the Netherlands. Journal of bone and joint infection **2016**; 1: 20-4.
29. Johnson AJ, Zywiel MG, Jones LC, Delanois RE, Stroh DA, Mont MA. Reduced re-infection rates with postoperative oral antibiotics after two-stage revision hip arthroplasty. BMC Musculoskelet Disord **2013**; 14: 123.
30. Zywiel MG, Johnson AJ, Stroh DA, Martin J, Marker DR, Mont MA. Prophylactic oral antibiotics reduce reinfection rates following two-stage revision total knee arthroplasty. Int Orthop **2011**; 35(1): 37-42.
31. Frank JM, Kayupov E, Moric M, et al. The Mark Coventry, MD, Award: Oral Antibiotics Reduce Reinfection After Two-Stage Exchange: A Multicenter, Randomized Controlled Trial. Clin Orthop Relat Res **2017**; 475(1): 56-61.
32. Karlsen Ø E, Borgen P, Bragnes B, et al. Rifampin combination therapy in staphylococcal prosthetic joint infections: a randomized controlled trial. Journal of orthopaedic surgery and research **2020**; 15(1): 365.
33. Ascione T, Pagliano P, Mariconda M, et al. Factors related to outcome of early and delayed prosthetic joint infections. The Journal of infection **2015**; 70(1): 30-6.
34. Ascione T, Pagliano P, Balato G, Mariconda M, Rotondo R, Esposito S. Oral Therapy, Microbiological Findings, and Comorbidity Influence the Outcome of Prosthetic Joint Infections Undergoing 2-Stage Exchange. J Arthroplasty **2017**; 32(7): 2239-43.
35. Senneville E, Joulie D, Legout L, et al. Outcome and predictors of treatment failure in total hip/knee prosthetic joint infections due to Staphylococcus aureus. Clin Infect Dis **2011**; 53(4): 334-40.
36. Becker A, Kreitmann L, Triffaut-Fillit C, et al. Duration of rifampin therapy is a key determinant of improved outcomes in early-onset acute prosthetic joint infection due to Staphylococcus treated with a debridement, antibiotics and implant retention (DAIR): a retrospective multicenter study in France. Journal of bone and joint infection **2020**; 5(1): 28-34.
37. Drancourt M, Stein A, Argenson JN, Roiron R, Groulier P, Raoult D. Oral treatment of Staphylococcus spp. infected orthopaedic implants with fusidic acid or ofloxacin in combination with rifampicin. Journal of Antimicrobial Chemotherapy **1997**; 39(2): 235-40.
38. Holmberg A, Thorhallsdottir VG, Robertsson O, A WD, Stefansdottir A. 75% success rate after open debridement, exchange of tibial insert, and antibiotics in knee prosthetic joint infections. Acta Orthop **2015**; 86(4): 457-62.
39. Lesens O, Ferry T, Forestier E, et al. Should we expand the indications for the DAIR (debridement, antibiotic therapy, and implant retention) procedure for Staphylococcus aureus prosthetic joint infections? A multicenter retrospective study. Eur J Clin Microbiol Infect Dis **2018**; 37(10): 1949-56.
40. Lora-Tamayo J, Murillo O, Iribarren JA, et al. A large multicenter study of methicillin-susceptible and methicillin-resistant Staphylococcus aureus prosthetic joint infections managed with implant retention. Clin Infect Dis **2013**; 56(2): 182-94.
41. Tornero E, Morata L, Martinez-Pastor JC, et al. Importance of selection and duration of antibiotic regimen in prosthetic joint infections treated with debridement and implant retention. The Journal of antimicrobial chemotherapy **2016**; 71(5): 1395-401.
42. Scheper H, Gerritsen LM, Pijls BG, Van Asten SA, Visser LG, De Boer MGJ. Outcome of Debridement, Antibiotics, and Implant Retention for Staphylococcal Hip and Knee Prosthetic Joint Infections,

Focused on Rifampicin Use: A Systematic Review and Meta-Analysis. Open Forum Infect Dis **2021**; 8(7): ofab298.
43. Aydın O, Ergen P, Ozturan B, Ozkan K, Arslan F, Vahaboglu H. Rifampin-accompanied antibiotic regimens in the treatment of prosthetic joint infections: a frequentist and Bayesian meta-analysis of current evidence. European Journal of Clinical Microbiology & Infectious Diseases **2021**; 40(4): 665-71.
44. Zimmerli W, Widmer AF, Blatter M, Frei R, Ochsner PE. Role of rifampin for treatment of orthopedic implant-related staphylococcal infections: a randomized controlled trial. Foreign-Body Infection (FBI) Study Group. Jama **1998**; 279(19): 1537-41.
45. Wouthuyzen-Bakker M, Tornero E, Morata L, et al. Moxifloxacin plus rifampin as an alternative for levofloxacin plus rifampin in the treatment of a prosthetic joint infection with Staphylococcus aureus. Int J Antimicrob Agents **2018**; 51(1): 38-42.
46. Dijkmans AC, Hartigh J, van Dissel JT, Burggraaf J. A simplified oral flucloxacillin absorption test for patients requiring long-term treatment. Ther Drug Monit. 2012;34(3):356-8.
47. Drancourt M, Stein A, Argenson JN, Zannier A, Curvale G, Raoult D. Oral rifampin plus ofloxacin for treatment of Staphylococcus-infected orthopedic implants. Antimicrobial Agents and Chemotherapy **1993**; 37(6): 1214-8.
48. Murillo O, Garrigos C, Pachon ME, et al. Efficacy of high doses of daptomycin versus alternative therapies against experimental foreign-body infection by methicillin-resistant Staphylococcus aureus. Antimicrob Agents Chemother **2009**; 53(10): 4252-7.
49. Byren I, Rege S, Campanaro E, et al. Randomized controlled trial of the safety and efficacy of Daptomycin versus standard-of-care therapy for management of patients with osteomyelitis associated with prosthetic devices undergoing two-stage revision arthroplasty. Antimicrob Agents Chemother **2012**; 56(11): 5626-32.
50. Telles JP, Cieslinski J, Tuon FF. Daptomycin to bone and joint infections and prosthesis joint infections: a systematic review. Braz J Infect Dis **2019**; 23(3): 191-6.
51. Gerritsen LM, Scheper H, de Boer MGJ, Schoones JW, Nelissen RGHH, Pijls BGC. Outcome of debridement, antibiotics and implant retention for streptococcal hip and knee prosthetic joint infections: A systematic review and meta-analysis. Surg Pract Sci. **2023**;14.
52. Mahieu R, Dubee V, Seegers V, et al. The prognosis of streptococcal prosthetic bone and joint infections depends on surgical management-A multicenter retrospective study. Int J Infect Dis **2019**; 85: 175-81.
53. Fiaux E, Titecat M, Robineau O, et al. Outcome of patients with streptococcal prosthetic joint infections with special reference to rifampicin combinations. BMC infectious diseases **2016**; 16(1): 568.
54. Wouthuyzen-Bakker M, Sebillotte M, Lomas J, et al. Clinical outcome and risk factors for failure in late acute prosthetic joint infections treated with debridement and implant retention. The Journal of infection **2019**; 78(1): 40-7.
55. Lora-Tamayo J, Senneville E, Ribera A, et al. The Not-So-Good Prognosis of Streptococcal Periprosthetic Joint Infection Managed by Implant Retention: The Results of a Large Multicenter Study. Clin Infect Dis **2017**; 64(12): 1742-52.
56. Zeller V, Lavigne M, Leclerc P, et al. Group B streptococcal prosthetic joint infections: a retrospective study of 30 cases. Presse medicale (Paris, France : 1983) **2009**; 38(11): 1577-84.
57. Kheir MM, Tan TL, Higuera C, et al. Periprosthetic Joint Infections Caused by Enterococci Have Poor Outcomes. J Arthroplasty **2017**; 32(3): 933-47.
58. Tornero E, Senneville E, Euba G, et al. Characteristics of prosthetic joint infections due to Enterococcus sp. and predictors of failure: a multi-national study. Clin Microbiol Infect **2014**; 20(11): 1219-24.
59. Renz N, Trebse R, Akgun D, Perka C, Trampuz A. Enterococcal periprosthetic joint infection: clinical and microbiological findings from an 8-year retrospective cohort study. BMC infectious diseases **2019**; 19(1): 1083.
60. El Helou OC, Berbari EF, Marculescu CE, et al. Outcome of enterococcal prosthetic joint infection: is combination systemic therapy superior to monotherapy? Clin Infect Dis **2008**; 47(7): 903-9.
61. Thompson O, Rasmussen M, Stefansdottir A, Christensson B, Akesson P. A population-based study on the treatment and outcome of enterococcal prosthetic joint infections. A consecutive series of 55 cases. Journal of bone and joint infection **2019**; 4(6): 285-91.
62. Corona Perez-Cardona PS, Barro Ojeda V, Rodriguez Pardo D, et al. Clinical experience with daptomycin for the treatment of patients with knee and hip periprosthetic joint infections. The Journal of antimicrobial chemotherapy **2012**; 67(7): 1749-54.

63. Yuste JR, Quesada M, Diaz-Rada P, Del Pozo JL. Daptomycin in the treatment of prosthetic joint infection by Enterococcus faecalis: safety and efficacy of high-dose and prolonged therapy. Int J Infect Dis **2014**; 27: 65-6.
64. Euba G, Lora-Tamayo J, Murillo O, et al. Pilot study of ampicillin-ceftriaxone combination for treatment of orthopedic infections due to Enterococcus faecalis. Antimicrob Agents Chemother **2009**; 53(10): 4305-10.
65. Yassien M, Khardori N, Ahmedy A, Toama M. Modulation of biofilms of Pseudomonas aeruginosa by quinolones. Antimicrob Agents Chemother **1995**; 39(10): 2262-8.
66. Abdi-Ali A, Mohammadi-Mehr M, Agha Alaei Y. Bactericidal activity of various antibiotics against biofilm-producing Pseudomonas aeruginosa. Int J Antimicrob Agents **2006**; 27(3): 196-200.
67. Di Bonaventura G, Spedicato I, D'Antonio D, Robuffo I, Piccolomini R. Biofilm formation by Stenotrophomonas maltophilia: modulation by quinolones, trimethoprim-sulfamethoxazole, and ceftazidime. Antimicrob Agents Chemother **2004**; 48(1): 151-60.
68. Rodriguez-Pardo D, Pigrau C, Lora-Tamayo J, et al. Gram-negative prosthetic joint infection: outcome of a debridement, antibiotics and implant retention approach. A large multicentre study. Clin Microbiol Infect **2014**; 20(11): O911-9.
69. Martinez-Pastor JC, Munoz-Mahamud E, Vilchez F, et al. Outcome of acute prosthetic joint infections due to gram-negative bacilli treated with open debridement and retention of the prosthesis. Antimicrobial Agents and Chemotherapy **2009**; 53(11): 4772-7.
70. Aboltins CA, Dowsey MM, Buising KL, et al. Gram-negative prosthetic joint infection treated with debridement, prosthesis retention and antibiotic regimens including a fluoroquinolone. Clinical Microbiology and Infection **2011**; 17(6): 862-7.
71. Hsieh PH, Lee MS, Hsu KY, Chang YH, Shih HN, Ueng SW. Gram-negative prosthetic joint infections: risk factors and outcome of treatment. Clin Infect Dis **2009**; 49(7): 1036-43.
72. Grossi O, Asseray N, Bourigault C, et al. Gram-negative prosthetic joint infections managed according to a multidisciplinary standardized approach: risk factors for failure and outcome with and without fluoroquinolones. The Journal of antimicrobial chemotherapy **2016**; 71(9): 2593-7.
73. Oprica C, Nord CE, Bacteria ESGoARiA. European surveillance study on the antibiotic susceptibility of Propionibacterium acnes. Clin Microbiol Infect **2005**; 11(3): 204-13.
74. Achermann Y, Goldstein EJ, Coenye T, Shirtliff ME. Propionibacterium acnes: from commensal to opportunistic biofilm-associated implant pathogen. Clin Microbiol Rev **2014**; 27(3): 419-40.
75. Tafin FU, Corvec S, Betrisey B, Zimmerli W, Trampuz A. Role of rifampin against Propionibacterium acnes biofilm in vitro and in an experimental foreign-body infection model. Antimicrob Agents Chemother **2012**; 56(4): 1885-91.
76. Jacobs AM, Van Hooff ML, Meis JF, Vos F, Goosen JH. Treatment of prosthetic joint infections due to Propionibacterium. Similar results in 60 patients treated with and without rifampicin. Acta Orthop **2016**; 87(1): 60-6.
77. Piggott DA, Higgins YM, Melia MT, et al. Characteristics and Treatment Outcomes of Propionibacterium acnes Prosthetic Shoulder Infections in Adults. Open Forum Infect Dis **2015**; 3(1): ofv191.
78. Kusejko K, Aunon A, Jost B, et al. The Impact of Surgical Strategy and Rifampin on Treatment Outcome in Cutibacterium Periprosthetic Joint Infections. Clin Infect Dis **2021**; 72(12): e1064-e73.
79. Cornely OA, Bassetti M, Calandra T, et al. ESCMID* guideline for the diagnosis and management of Candida diseases 2012: non-neutropenic adult patients. Clin Microbiol Infect **2012**; 18 Suppl 7: 19-37.
80. Stichting Werkgroep Antibioticabeleid (SWAB). SWAB Guidelines for the Management of Invasive Fungal Infections. Available at: https://swab.nl/exec/file/download/86. Accessed June 12.
81. Felton T, Troke PF, Hope WW. Tissue penetration of antifungal agents. Clin Microbiol Rev **2014**; 27(1): 68-88.
82. Kim SJ, Huh J, Odrobina R, Kim JH. Systemic review of published literature on Candida infection following total hip arthroplasty. Mycopathologia **2015**; 179(3-4): 173-85.
83. Koutserimpas C, Zervakis SG, Maraki S, et al. Non-albicans Candida prosthetic joint infections: A systematic review of treatment. World journal of clinical cases **2019**; 7(12): 1430-43.
84. McNally M, Sousa R, Wouthuyzen-Bakker M, Chen AF, Soriano A, Vogely HC, et al. The EBJIS definition of periprosthetic joint infection. Bone Joint J. **2021**;103-B(1):18-25.
85. Yoon HK, Cho SH, Lee DY, et al. A Review of the Literature on Culture-Negative Periprosthetic Joint Infection: Epidemiology, Diagnosis and Treatment. Knee Surg Relat Res **2017**; 29(3): 155-64.

86. Santoso A, Park KS, Shin YR, Yang HY, Choi IS, Yoon TR. Two-stage revision for periprosthetic joint infection of the hip: Culture-negative versus culture-positive infection. J Orthop **2018**; 15(2): 391-5.
87. Ibrahim MS, Twaij H, Haddad FS. Two-stage revision for the culture-negative infected total hip arthroplasty : A comparative study. Bone Joint J **2018**; 100(1): 3-8.
88. Reisener M, Perka C. Do Culture-Negative Periprosthetic Joint Infections Have a Worse Outcome Than Culture-Positive Periprosthetic Joint Infections? A Systematic Review and Meta-Analysis. Biomed Res Int **2018**; 2018: 6278012.
89. Wang J, Wang Q, Shen H, Zhang X. Comparable outcome of culture-negative and culture-positive periprosthetic hip joint infection for patients undergoing two-stage revision. Int Orthop **2018**; 42(3): 469-77.
90. Huang R, Hu CC, Adeli B, Mortazavi J, Parvizi J. Culture-negative periprosthetic joint infection does not preclude infection control. Clin Orthop Relat Res **2012**; 470(10): 2717-23.
91. Pavoni GL, Giannella M, Falcone M, et al. Conservative medical therapy of prosthetic joint infections: retrospective analysis of an 8-year experience. Clin Microbiol Infect **2004**; 10(9): 831-7.
92. Senthi S, Munro JT, Pitto RP. Infection in total hip replacement: Meta-analysis. International Orthopaedics **2011**; 35(2): 253-60.
93. Darley ESR, Bannister GC, Blom AW, Macgowan AP, Jacobson SK, Alfouzan W. Role of early intravenous to oral antibiotic switch therapy in the management of prosthetic hip infection treated with one- or two-stage replacement. Journal of Antimicrobial Chemotherapy **2011**; 66(10): 2405-8.
94. SWAB guidelines for the antimicrobial treatment of infective endocarditis. **2019**.
95. Lora-Tamayo J, Euba G, Cobo J, et al. Short- versus long-duration levofloxacin plus rifampicin for acute staphylococcal prosthetic joint infection managed with implant retention: a randomised clinical trial. Int J Antimicrob Agents **2016**; 48(3): 310-6.
96. Chaussade H, Uckay I, Vuagnat A, et al. Antibiotic therapy duration for prosthetic joint infections treated by Debridement and Implant Retention (DAIR): Similar long-term remission for 6 weeks as compared to 12 weeks. Int J Infect Dis **2017**; 63: 37-42.
97. Puhto AP, Puhto T, Syrjala H. Short-course antibiotics for prosthetic joint infections treated with prosthesis retention. Clin Microbiol Infect **2011**; 18(11): 1143-8.
98. Bernard L, Legout L, Zurcher-Pfund L, et al. Six weeks of antibiotic treatment is sufficient following surgery for septic arthroplasty. Journal of Infection **2010**; 61(2): 125-32.
99. Yen HT, Hsieh RW, Huang CY, et al. Short-course versus long-course antibiotics in prosthetic joint infections: A systematic review and meta-analysis of one randomized controlled trial plus nine observational studies. Journal of Antimicrobial Chemotherapy **2019**; 74(9): 2507-16.
100. Ilchmann T, Zimmerli W, Ochsner PE, et al. One-stage revision of infected hip arthroplasty: outcome of 39 consecutive hips. Int Orthop **2016**; 40(5): 913-8.
101. Stockley I, Mockford BJ, Hoad-Reddick A, Norman P. The use of two-stage exchange arthroplasty with depot antibiotics in the absence of long-term antibiotic therapy in infected total hip replacement. The Journal of bone and joint surgery British volume **2008**; 90(2): 145-8.
102. Bernard L, Arvieux C, Brunschweiler B, et al. Antibiotic Therapy for 6 or 12 Weeks for Prosthetic Joint Infection. The New England journal of medicine **2021**; 384(21): 1991-2001.
103. Bene N, Li X, Nandi S. Increased antibiotic duration improves reoperation free survival after total hip arthroplasty irrigation and debridement. Journal of Orthopaedics **2018**; 15(2): 707-10.
104. Chieffo G, Corsia S, Rougereau G, et al. Six-week antibiotic therapy after one-stage replacement arthroplasty for hip and knee periprosthetic joint infection. Med Mal Infect **2020**; 50(7): 567-74.
105. Spitzmuller R, Gumbel D, Guthoff C, et al. Duration of antibiotic treatment and risk of recurrence after surgical management of orthopaedic device infections: A multicenter case-control study. BMC Musculoskeletal Disorders **2019**; 20(184).
106. Ascione T, Balato G, Mariconda M, Rotondo R, Baldini A, Pagliano P. Continuous Antibiotic Therapy Can Reduce Recurrence of Prosthetic Joint Infection in Patients Undergoing 2-Stage Exchange. J Arthroplasty **2019**; 34(4): 704-9.
107. Tan TL, Kheir MM, Rondon AJ, et al. Determining the Role and Duration of the "Antibiotic Holiday" Period in Periprosthetic Joint Infection. J Arthroplasty **2018**; 33(9): 2976-80.
108. Achermann Y, Eigenmann K, Ledergerber B, et al. Factors associated with rifampin resistance in staphylococcal periprosthetic joint infections (PJI): a matched case-control study. Infection **2013**; 41(2): 431-7.

109. Beldman M, Lowik C, Soriano A, et al. If, When, and How to Use Rifampin in Acute Staphylococcal Periprosthetic Joint Infections, a Multicentre Observational Study. Clin Infect Dis **2021**; 73(9): 1634-41.
110. Scheper H, van der Wal RJP, Mahdad R, Keizer S, Delfos NM, van der Lugt JCT, et al. Effectiveness of Different Antimicrobial Strategies for Staphylococcal Prosthetic Joint Infection: Results From a Large Prospective Registry-Based Cohort Study. Open Forum Infect Dis. **2022**;9(10):ofac474.
111. Tirumala V, Smith E, Box H, van den Kieboom J, Klemt C, Kwon YM. Outcome of Debridement, Antibiotics, and Implant Retention With Modular Component Exchange in Acute Culture-Negative Periprosthetic Joint Infections. J Arthroplasty. **2020**.
112. Choi HR, Kwon YM, Freiberg AA, Nelson SB, Malchau H. Periprosthetic joint infection with negative culture results: clinical characteristics and treatment outcome. J Arthroplasty. **2012**;28(6):899-903.
113. Escudero-Sanchez R, Senneville E, Digumber M, Soriano A, del Toro MD, Bahamonde A, et al. Suppressive antibiotic therapy in prosthetic joint infections: a multicentre cohort study. Clinical Microbiology and Infection. **2020**;26(4):499-505.
114. Leijtens B, Weerwag L, Schreurs BW, Kullberg BJ, Rijnen W. Clinical Outcome of Antibiotic Suppressive Therapy in Patients with a Prosthetic Joint Infection after Hip Replacement. Journal of bone and joint infection. **2019**;4(6):268-76.
115. Prendki V, Ferry T, Sergent P, Oziol E, Forestier E, Fraisse T, et al. Prolonged suppressive antibiotic therapy for prosthetic joint infection in the elderly: a national multicentre cohort study. Eur J Clin Microbiol Infect Dis. **2017**;36(9):1577-85.
116. Pradier M, Robineau O, Boucher A, Titecat M, Blondiaux N, Valette M, et al. Suppressive antibiotic therapy with oral tetracyclines for prosthetic joint infections: a retrospective study of 78 patients. Infection. **2018**;46(1):39-47.
117. Prendki V, Zeller V, Passeron D, Desplaces N, Mamoudy P, Stirnemann J, et al. Outcome of patients over 80 years of age on prolonged suppressive antibiotic therapy for at least 6 months for prosthetic joint infection. Int J Infect Dis. **2014**;29:184-9.
118. Rao N, Crossett LS, Sinha RK, Le Frock JL. Long-term suppression of infection in total joint arthroplasty. Clin Orthop Relat Res. **2003**(414):55-60.
119. Sandiford NA, Hutt JR, Kendoff DO, Mitchell PA, Citak M, Granger L. Prolonged suppressive antibiotic therapy is successful in the management of prosthetic joint infection. European journal of orthopaedic surgery & traumatology : orthopedie traumatologie. **2020**;30(2):313-21.
120. Wouthuyzen-Bakker M, Nijman JM, Kampinga GA, van Assen S, Jutte PC. Efficacy of Antibiotic Suppressive Therapy in Patients with a Prosthetic Joint Infection. Journal of bone and joint infection. **2017**;2(2):77-83.
121. Malahias MA, Gu A, Harris EC, Adriani M, Miller AO, Westrich GH, Sculco PK. The Role of Long-Term Antibiotic Suppression in the Management of Peri-Prosthetic Joint Infections Treated With Debridement, Antibiotics, and Implant Retention: A Systematic Review. J Arthroplasty. **2020**;35(4):1154-60.
122. Ma HH, Chou TA, Tsai SW, Chen CF, Wu PK, Chen CM, Chen WM. Is short-course systemic antibiotic therapy using an antibiotic-loaded cement spacer safe after resection for infected total knee arthroplasty? A comparative study. Journal of the Formosan Medical Association = Taiwan yi zhi. **2020**;119(6):1070-9.
123. El Helou OC, Berbari EF, Lahr BD, Marculescu CE, Razonable RR, Steckelberg JM, et al. Management of prosthetic joint infection treated with two-stage exchange: the impact of antimicrobial therapy duration. Current Orthopaedic Practice. **2011**;22(4):333-8.
124. Benkabouche M, Racloz G, Spechbach H, Lipsky BA, Gaspoz JM, Uckay I. Four versus six weeks of antibiotic therapy for osteoarticular infections after implant removal: a randomized trial. The Journal of antimicrobial chemotherapy. **2019**;74(8):2394-9.