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Antibioticabeleid

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

Guideline committee

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NVMM: Nederlandse Vereniging voor Medische Microbiologie (Dutch Society of Medical Microbiology); NIV: Nederlandse Internisten Vereniging (Dutch Society of Internal Medicine); NVII: Nederlandse Vereniging voor Internist-infectiologen (Dutch Society for Infectious Diseases); NVZA: Nederlandse Vereniging van Ziekenhuisapothekers (Dutch Society of Hospital Pharmacists); NOV: Nederlandse Orthopaedische Vereniging (Dutch Orthopaedic Association)

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Part I: General principles

Introduction

5 An infection of a prosthetic joint is a serious complication, carrying high morbidity and mortality for the patient and substantial health care costs. Of the 64,000 patients in the Netherlands who undergo hip or knee arthroplasty each year, about 1.5-2.0% end up with an infection.[1] Infection is the main reason for hip revision within one year after arthroplasty.[1] The incidence of periprosthetic joint infections (PJI) is expected to increase in the years to come with the ageing of society, an increasing
10 number of primary implantations being performed and the number of cumulative arthroplasties that remain in place.[2]

Traditionally the management of PJI includes resection arthroplasty or removal of fixation devices, in combination with tailored (short term) antibiotic treatment based on susceptibility test results.
15 However, as the population with prosthetic joints gets older and the surgical options more profound, long-term antibiotics are often used in conjunction with surgical debridement and implant retention. 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
20 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
25 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
30 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

35 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. For these topics, we refer to the guidelines of the Dutch Orthopaedic Society,[6] the practice guidelines of the Infectious Diseases Society of America,
40 [3] and the international consensus documents.[5, 7, 8]

Methods

The guideline was written according to the Appraisal of Guidelines for Research & Evaluation (AGREE)
45 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 31 clinical questions (see Appendix A) of importance in current Dutch practices. Among these were questions about empirical therapy for PJI, culture directed therapy, dosing of antimicrobials and the timing and duration of therapy. Due to the applicability or urgency of the questions, the amount of evidence available and the frequency of occurrence, the guideline committee decided to do a systematic literature search for 16 of the developed clinical questions. 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 members. Discrepancies between two committee members were resolved through discussion. 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'. The certainty of evidence, rated as 'high', 'moderate', 'low' or 'very low' 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 'best clinical practice'.

Preparation of the guideline text was carried out by a multidisciplinary committee consisting of experts delegated from their professional societies. The guideline committee was responsible for the preparation of this guideline. After consultation with the members of these professional societies in the Netherlands, we have 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.

There was no unanimous consensus 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 even higher dosages, comparable with dosages administered in other serious 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.

105 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.

110 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 | CN | Multiple cultures of both preoperative joint aspirate and intraoperative periprosthetic tissue samples did not lead to an isolated organism |
| Debridement, antibiotics and implant retention | DAIR | Treatment regimen for periprosthetic joint infection in which debridement, antibiotics and implant retention are combined |
| 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 <i>Staphylococcus aureus</i> | MRSA | <i>Staphylococcus aureus</i> resistant to methicillin and other beta lactam antibiotics (with the exception of fifth generation cephalosporins e.g., ceftaroline) |
| Methicillin-susceptible <i>Staphylococcus aureus</i> | MSSA | <i>Staphylococcus aureus</i> sensitive to methicillin and other beta lactam antibiotics |
| One-staged revision | 1SR | Surgical treatment for periprosthetic joint infection in which revision of the prosthesis is 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 an established PJI |
| Two-staged revision | 2SR | Surgical treatment for periprosthetic joint infection in which revision of the prosthesis is conducted in two procedures with short or long intervals between procedures |

115 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.

130 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.

135 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

140 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.

145 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 |
|----------------------|-------------------------------------|
| Dr. E.J.G. Peters | Roche Diagnostics, research funding |
| Dr. S.A.V. van Asten | None to declare |
| M. Wouthuyzen-Bakker | None to declare |
| H. Scheper | None te declare |
| E. van Elzaker | None to declare |
| L. Reubsaet | |
| Dr. M.W. Nijhof | None to declare |
| H. Vogely | |
| G. Van der Bij | |
| P. C. Jutte | None to declare |
| P.D. van der Linden | None to declare |
| A. Plender | None to declare |

150 **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.

155
160 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.

165 Part II: Synopsis of recommendations

General recommendations not based on PICOs and systematic review of literature

170 General principles of antimicrobial treatment of PJI

Recommendation:

We recommend administering antibiotic therapy for PJI initially by the parenteral route with continuous infusion whenever possible. Switch to oral therapy if the patient is clinically improving, has no contraindications to oral therapy and if there is an appropriate oral agent available with adequate bio-availability.

175 Good practice statement

Allergies to first choice antibiotics and toxicity

180 **Recommendation:**

We recommend to refer to the SWAB guideline in case of true antimicrobial allergies, for detailed information regarding the approach to (suspected) antibiotic allergies, and potential cross-reactivity of antibiotics.[13]

185 Good practice statement

Empirical therapy

Recommendation:

We suggest to select an empirical therapy for treating a PJI based on the suspected causative pathogens and their antibiotic susceptibilities. The prescriber should take into consideration previous culture results, previous treatments and the timing of the infection. Some agents to consider are: β -lactams in high dosages (flucloxacillin or cefazolin, third generation cephalosporins), aminoglycosides or vancomycin.

190 Good practice statement

195 **Recommendation:**

In case of early post-operative infection, we suggest to empirically cover *Staphylococcus aureus*, streptococci, coagulase negative staphylococci, enterococci, Enterobacterales, *Pseudomonas*, and to not cover resistant bacteria including MRSA and resistant gram negative bacteria (when there are no risk factors or previous cultures suggesting that these organisms cause the infection).

200 Good practice statement

Recommendation:

In case of late acute (haematogenous) infection, we suggest to empirically cover *Staphylococcus aureus*, streptococci and Enterobacterales (when there are no risk factors or previous cultures suggesting that other organisms cause the infection).

205 Good practice statement

Recommendation:

210 In case of late chronic infection, we suggest to empirically cover coagulase negative staphylococci, enterococci, *Cutibacterium acnes* (when there are no risk factors or previous cultures suggesting that other organisms cause the infection).
Good practice statement

215 **Specific recommendations based on PICOs and systematic review of literature**

Culture directed antimicrobial therapy

Staphylococci

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

Recommendation:

225 We suggest to add rifampicin in the treatment of (rifampicin-susceptible) staphylococcal PJI
Strength of recommendation: conditional, level of evidence: moderate

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?

230

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, level of evidence: moderate

235

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?

240 **Recommendation:**

We suggest to use vancomycin, not daptomycin, as first choice of treatment for PJI caused by methicillin resistant staphylococci.
Strength of recommendation: conditional, level of evidence: very low

245 ***Streptococci***

PICO 2a: In a person with a PJI caused by streptococci, is a rifampicin-based regimen more effective in achieving clinical cure?

250 **Recommendation:**

We suggest not to use rifampicin for streptococcal PJI.
Strength of recommendation: conditional, level of evidence: low

255 **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.

260 Strength of recommendation: conditional, level of evidence: very low

Enterococci

265 **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.

270 Strength of recommendation: conditional, level of evidence: low

Recommendation:

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

275 Strength of recommendation: conditional, level of evidence: low

Gram-negative bacilli

280 **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.

285 Strength of recommendation: strong, level of evidence: moderate

290

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?

295

Recommendation:

We suggest to treat *Cutibacterium acnes* PJI with amoxicillin.

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

300

PICO 5b: In a person with a PJI caused by *Cutibacterium (Propionibacterium) acnes*, is a rifampicin-based regimen more effective in achieving clinical cure?

305 **Recommendation:**

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

310 **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?

315 **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.

Strength of recommendation: conditional, level of evidence: low

320

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?

325

Recommendation:

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

330 Strength of recommendation: conditional, level 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)

335 Strength of recommendation: strong, level 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?

340

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)

345 Strength of recommendation: conditional, level of evidence: very low

Recommendation:

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

350 Strength of recommendation: conditional, level of evidence: very low

Duration of therapy, route of administration and dosages

355 **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:

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

365 **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:

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

Timing of therapy

375 **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:

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

385 **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:

390 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, level of evidence: very low.

Recommended empirical antimicrobial treatment

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

| Surgical strategy | | Penicillin allergy |
|---|---|---|
| DAIR for early acute PJI / 1SR for late chronic PJI | vancomycin 45 mg/kg continuously /24 hr (20 mg/kg loading dose) i.v. OR 1000 mg TID i.v. ^b + ceftazidime 6 g/ 24 i.v. (loading dose 2 g).hr | |
| 2SR (after explantation) / girdlestone | flucloxacillin i.v. 6 gram/24h i.v. (after loading dose 1 gram) ^c | vancomycin 45 mg/kg continuously /24 hr (20 mg/kg loading dose) i.v. OR 1000 mg TID i.v. ^b |

Dosing is always adjusted to renal function.

^a antibiotic strategy may be changed in case of MRSA/MDRO colonisation

^b therapeutic drug monitoring (TDM) serum vancomycin trough 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)

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

Recommended targeted antimicrobial treatment for common microorganisms causing PJI

Table 4 Targeted antimicrobial treatment for PJI

| Causative microorganism | First choice treatment | Second choice(s) of treatment in oral treatment phase | Penicillin allergy |
|---|--|---|---|
| DAIR or 1SR | | | |
| <i>S. aureus</i> - MSSA CNS - flucloxacillin | flucloxacillin 6 g/24h i.v. (after loading dose 1 gram) † for 1-2 weeks + | clindamycin 600 mg TID or trimethoprim-sulfamethoxazole 960 | cefazolin 4 g/24h i.v. † (after loading dose of 1 gram for 1-2 weeks + |

| | | | |
|---|---|--|--|
| sensitive | rifampicin 450 mg BID p.o (or i.v.) † <i>followed by</i> rifampicin 450 mg BID p.o. † + levofloxacin 500 mg BID p.o. (levofloxacin can be replaced by ciprofloxacin 750mg BID po) | mg BID † <i>or</i> flucloxacillin 1000 mg 5 times daily p.o. (only if adequate absorption test) | rifampicin 450 mg BID p.o (or i.v.) † <i>followed by</i> rifampicin 450 mg BID p.o. + levofloxacin 500 mg BID p.o. (levofloxacin can be replaced by ciprofloxacin 750mg BID po) |
| <i>S. aureus</i> - MRSA CNS - flucloxacillin resistant | vancomycin 45 mg/kg continuously /24 hr (20 mg/kg loading dose) OR 1000 mg TID* for 1-2 weeks <i>and</i> rifampicin 450 mg BID p.o. or i.v. † <i>followed by</i> rifampicin 450 mg BID p.o. † + levofloxacin 500 mg BID p.o. (levofloxacin can be replaced by ciprofloxacin 500 mg BID po † or moxifloxacin 400 mg OD) | rifampicin 450 mg BID † + clindamycin 600 mg TID <i>or</i> rifampicin 450 mg BID † + trimethoprim-sulfamethoxazole 960 mg BID † | |
| <i>Enterobacteriales</i> (e.g., <i>E. coli</i> , <i>Klebsiella</i> , <i>Proteus</i>) | ceftriaxone 2 gram OD i.v. for 1-2 weeks <i>followed by</i> ciprofloxacin 500 mg BID p.o. † | trimethoprim-sulfamethoxazole 960 mg BID i.v. or p.o. † | |
| <i>P. aeruginosa</i> | ceftazidime 6 g/24hours i.v. (after loading dose 2 g) for 1-2 weeks | | |

| | | | |
|--|--|-----------------------------|---|
| | <i>followed by</i> ciprofloxacin 750 mg BID p.o. | | |
| <i>C. acnes</i> | penicillin G 6MU/24h i.v. † (after loading dose 1MU) for 1-2 weeks <i>followed by</i> amoxicillin 1000 mg TID p.o. | clindamycin 600 mg TID p.o. | ceftriaxone 2000 mg/24h i.v <i>Followed by</i> Clindamycin 600 mg TID p.o. |
| <i>Streptococcus</i> | penicillin G 6MU † /24h i.v. (after loading dose 1MU) for 1-2 weeks <i>followed by</i> amoxicillin 1000 mg TID p.o. | clindamycin 600 mg TID p.o. | Ceftriaxone 2000 mg/24h i.v <i>Followed by</i> Clindamycin 600 mg TID p.o. |
| <i>Enterococcus</i> - Amoxicillin susceptible | amoxicillin 6 g/24h IV for 2 weeks, † after loading dose of 1 g. <i>and</i> ceftriaxone 2 gram BID for 2 weeks <i>or:</i> amoxicillin monotherapy 6 g/24 hr iv for two weeks † after loading dose of 1 g. <i>followed by</i> amoxicillin 1000 mg TID p.o. | linezolid 600 mg p.o. BID | vancomycin 45 mg/kg continuously /24 hr (20 mg/kg loading dose) OR 1000 mg TID for 1-2 weeks <i>(Followed by</i> Linezolid 600 mg BID p.o. or continuous vancomycin iv therapy) |
| <i>Enterococcus</i> - Amoxicillin resistant | Monotherapy vancomycin 45 mg/kg continuously /24 hr (20 mg/kg loading dose) OR 1000 mg TID * for 1-2 weeks <i>followed by</i> linezolid 600 mg BID | linezolid 600 mg p.o. BID. | |

| | | | |
|---|---|---|--|
| Anaerobe gram negative | Metronidazole 500 mg TID | Clindamycin 600 mg TID | |
| <i>Candida</i> - Fluconazole susceptible | Fluconazole 400 mg OD, loading dose 800 mg i.v. after 1-2 weeks followed by: Fluconazole 400 mg p.o. OD | | |
| <i>Candida</i> - Fluconazole resistant | liposomal amphotericin B 3 mg/kg OD i.v. <i>or:</i> Anidulafungin 100 mg OD, loading dose 200 mg <i>or</i> Caspofungin 50 mg OD (70 mg if body weight > 80 kg), loading dose 70 mg <i>or</i> Miconazole 100 mg OD | | |
| | | | |
| Culture-negative | discuss in multidisciplinary team | | |
| 2SR after explantation | | | |
| <i>S. aureus</i> - MSSA CNS - flucloxacillin sensitive | flucloxacillin 6 g/24h i.v. † (after loading dose 1 gram) for 1-2 weeks followed by: clindamycin 600 mg TID | trimethoprim-sulfamethoxazole 960mg BID † <i>or</i> flucloxacillin 1000mg 5 times daily p.o. (only if adequate absorption test) | cefazolin 4 g/24h i.v. † (after loading dose 1 gram) for 1-2 weeks followed by: clindamycin 600 mg TID |

| | | | |
|---|---|---------------------------|---|
| <i>S. aureus</i> - MRSA CNS - flucloxacillin resistant | vancomycin 45 mg/kg continuously /24 hr i.v. (20 mg/kg loading dose) OR 1000 mg TID * for 1-2 weeks Or daptomycin 10 mg/kg i.v. OD <i>followed by</i> clindamycin 600 mg TID p.o. <i>or</i> trimethoprim-sulfamethoxazole 960mg BID p.o. † | | |
| Enterobacterales and <i>Pseudomonas</i> | see targeted therapy for DAIR or 1SR | | |
| <i>C. acnes</i> | see targeted therapy for DAIR or 1SR | | |
| <i>Streptococcus</i> | see targeted therapy for DAIR or 1SR | | |
| <i>Enterococcus</i> - Amoxicillin susceptible | amoxicillin 6g/24h IV for 2 weeks, † after loading dose of 1 g. <i>followed by</i> amoxicillin 1000 mg TID p.o. | linezolid 600 mg p.o. BID | vancomycin 45 mg/kg continuously /24 hr (20 mg/kg loading dose) |
| <i>Enterococcus</i> - Amoxicillin resistant | see targeted therapy for DAIR or 1SR | | |
| Anaerobe gram negative | see targeted therapy for DAIR or 1SR | | |

| | | | |
|--|--------------------------------------|--|------------------------|
| <i>Candida</i> - Fluconazole susceptible | see targeted therapy for DAIR or 1SR | | |
| <i>Candida</i> - Fluconazole resistant | 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 | |
| <i>S. aureus</i> - MSSA CNS - flucloxacillin sensitive | flucloxacillin 1000 mg BID | clindamycin 600 mg BID <i>or</i> trimethoprim-sulfamethoxazole 960mg OD <i>or</i> doxycycline 100 mg OD <i>or</i> azithromycin 500 mg three times per week | |
| <i>S. aureus</i> - MRSA CNS - flucloxacillin resistant | clindamycin 600 mg BID | trimethoprim-sulfamethoxazole 960mg OD <i>or</i> doxycycline 100mg OD <i>or</i> azithromycin 500 mg three times per week | |
| <i>C. acnes</i> | amoxicillin 1000 mg BID | clindamycin 600 mg BID | Clindamycin 600 mg BID |

| | | | |
|--|---|------------------------|------------------------|
| Gram negative bacilli | trimethoprim-sulfamethoxazole 960mg OD | | |
| <i>Streptococcus</i> | amoxicillin 1000 mg BID | clindamycin 600 mg BID | Clindamycin 600 mg BID |
| <i>Enterococcus</i> - Amoxicillin susceptible | amoxicillin 1000 mg BID | | |
| <i>Candida</i> - Fluconazole susceptible | fluconazole 100 mg 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 minimally 6 weeks | | | |

1

2 General recommendations:

3 If a patient has a concomitant bacteremia, endocarditis or candidemia, we refer to the guidelines for the relevant SWAB guidelines.

4 Dosing always adjusted to renal function

5 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.

6 * therapeutic drug monitoring (TDM) serum vancomycin trough concentration in intermittent infusion > 15 mg/L, steady state concentration for continuous infusion 17-25 mg/L.

7 † Dose ranges:

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

11 Trimethoprim-sulfamethoxazole (co-trimoxazole) dose range 960 mg BID - 960 mg TID

12 Rifampicin dose range 450 mg BID - 600 mg BID

13 Cefazolin dose range 4-6 g / 24 hr

14 Ciprofloxacin dose range 500 mg BID - 750 mg BID for quinolone-sensitive organisms (e.g., Enterobacteriales). Dose for quinolone intermediate sensitivity organisms (e.g., *S. aureus* and *Pseudomonas* spp): 750 mg BID

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

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

2

3

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

CONCEPT

Part III: literature review and formulated recommendations

5 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 therefore highly recommended.

PJI should be suspected in all patients with persistent wound drainage, ongoing or acute onset of a painful prosthesis, or with a history of prior wound healing problems or infection.[3-6, 8] After a thorough history and physical examination, other modalities like serum biomarkers (C-reactive protein), synovial markers, histology, or imaging studies (plain radiographs) might be used to underline the suspicion.[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*). For the definite diagnosis, intraoperative histopathological and microbiological examination of tissue samples is needed, preferably without prior antibiotic treatment (especially in revisions with high suspicion for PJI with 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, with most of them using a symptom duration of 3 weeks as a cut-off point [3, 4] while others use 6 weeks [6], or separate an early post-surgery group (up to three months after placement of the prosthesis). 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 result in one- or two stage revisions, amputations or in rare cases suppressive therapy with implant retention. 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 with continuous infusion whenever possible. Switch to oral therapy if the patient is clinically improving, 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 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 refer to the SWAB guideline in case of true antimicrobial allergies, 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 are best kept in reserve to decrease antibiotic overuse, and thereby 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 deep into these modular components. Moreover, modular component exchange is advised because the polyethylene component (acetabular liner or tibial inlay) may be colonised by microorganisms. The soft tissue should be meticulously closed in a multilayer fashion.

5 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 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.

15 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 or more 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 and empirical antimicrobial treatment should be continued until culture results are definitive.[22]

20 4. Empirical therapy

Recommendation:

25 **We suggest to select an empirical therapy for treating a PJI based on the suspected causative pathogens and their antibiotic susceptibilities. The prescriber should take into consideration previous culture results, previous treatments and the timing of the infection. Some agents to consider are: β -lactams in high dosages (flucloxacillin or cefazolin, third generation cephalosporins), aminoglycosides or vancomycin.**

Good practice statement

30 ***Recommendation:***

In case of early post-operative infection, we suggest to empirically cover *Staphylococcus aureus*, streptococci, coagulase negative staphylococci, enterococci, Enterobacterales, *Pseudomonas* and to not cover resistant bacteria including MRSA and resistant gram negative bacteria (when there are no risk factors or previous cultures suggesting that these organisms cause the infection).

35 **Good practice statement**

Recommendation:

40 **In case of late acute (haematogenous) infection, we suggest to empirically cover *Staphylococcus aureus*, streptococci and Enterobacterales (when there are no risk factors or previous cultures suggesting that other organisms cause the infection).**

Good practice statement

Recommendation:

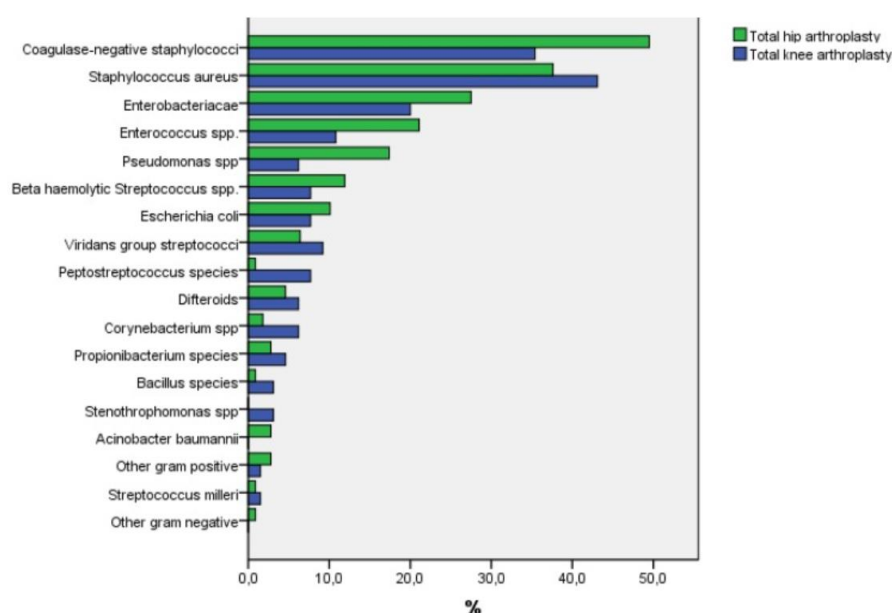
45 **In case of late chronic infection, we suggest to empirically cover coagulase negative staphylococci, enterococci, *Cutibacterium acnes* (when there are no risk factors or previous cultures suggesting that other organisms cause the infection).**

Good practice statement

50

Rationale

The 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 prevent new biofilm formation on the newly inserted foreign bodies. In case of 2SR, the foreign material is taken out, making biofilm formation less of an issue. As a result, empirical therapy in case of DAIR and 1SR has a broader spectrum and in case of 2SR it is aimed at only the more pathogenic bacteria pending the identification of the organism(s). Polymicrobial cultures often occur in early postoperative infections or (chronic) infections in the presence of a fistula, and need to be taken into consideration when choosing an empirical strategy. In Europe most PJIs are caused by coagulase-negative staphylococci (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. 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] Though the exact local resistance rates of gram-negative isolates to cephalosporins in PJI isolates in the Netherlands are not known, studies report a much lower rate than in the mentioned European studies.[27, 28] The question remains if a broader agent and anti-pseudomonal coverage in the empirical treatment needs to be considered.



25 Percentage micro organisms associated with PJI in THA and TKA.

Figure 1: microorganisms associated with PJI in total hip and total knee arthroplasties.

Copied from de Vries et al.[28]

30 In general, with early acute (postoperative) PJI more polymicrobial infections with staphylococci can be expected and because the surgery of choice is often DAIR (debridement, antibiotics and implant retention), empirical treatment should reduce the bacterial load in the shortest time possible and to prevent ongoing biofilm formation. 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 local susceptibility patterns and empirical treatment in the Netherlands. For practical purposes, flowchart Figure 2 sums up the parameters a clinician can use to target the empirical antimicrobial therapy. Table 3 shows an overview of recommended empirical antimicrobial treatment regimens for PJI, to be started after surgical debridement with intraoperative cultures.

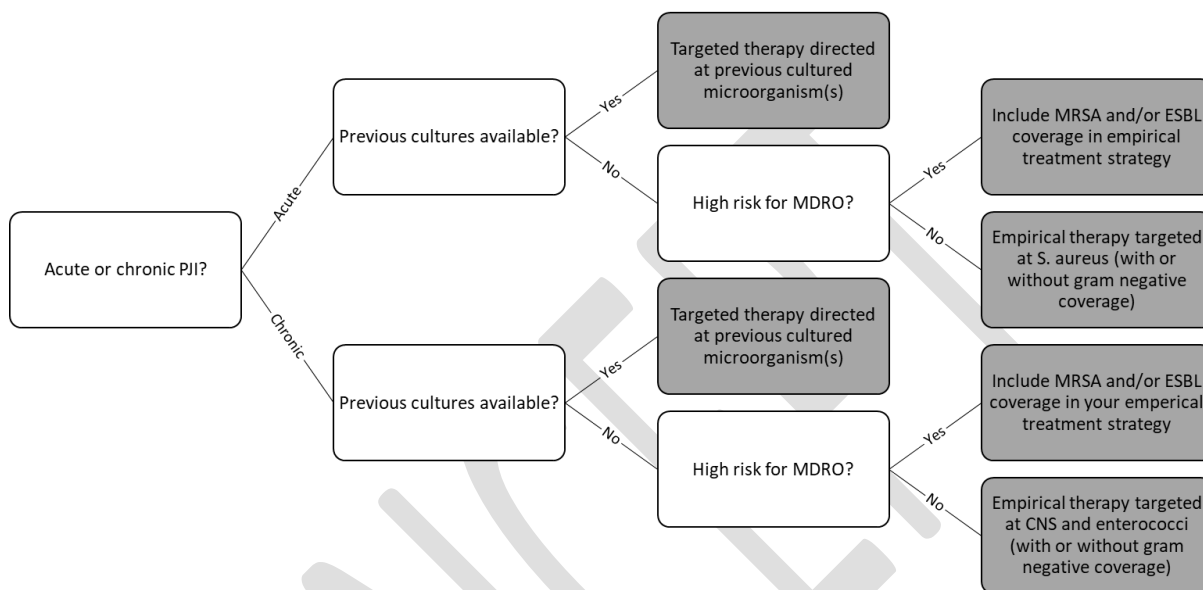


Figure 2: Flowchart showing parameters a clinician can use as a basis for the choice of empirical treatment for PJI.

MDRO=multidrug resistant organism, MRSA=Methicillin-resistant *S. aureus*. ESBL=Extended spectrum beta-lactamase producer. CNS=Coagulase-negative Staphylococcus

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 analysed evidence on the optimal treatment strategy for several microorganisms. Targeted therapy is summarized 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

Strength of recommendation: conditional, level of evidence: moderate

Rationale:

11 studies were included in the evidence tables in Appendix 3.

- 5 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]
- 10 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]
- 15 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]
- 20 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]
- 25 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]
- 30 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]
- 35 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.
- 40 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.
- 45 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]
- 50 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 well-known 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, played a major role because four of five failures in this group were 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).[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 ($p>0.5$).

Summary of evidence: There seems to be a larger proportion of patients with a preferable outcome with combination therapy with rifampicin in the treatment of staphylococcal PJI. Although there is one study that suggested that short durations of rifampicin lead to worse outcomes, the quality of evidence is too low to make recommendations on this. However, there is inconsistency in outcomes in trials and cohort studies to patients treated with or without rifampicin in combination with other antibiotics. Furthermore, the efficacy of rifampicin in these studies was often not studied in a single but rather 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. We did not find evidence to support adaptations of dosages of concomitantly administered antibiotics when rifampicin is given. The level of evidence is reduced to moderate based on the inconsistency of outcomes of RCTs (and 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. Given the inconsistency in results and the need for noninferior alternatives for rifampicin, a Dutch multicenter study will start in 2023 to evaluate whether monotherapy with clindamycin is noninferior to rifampicin/levofloxacin in the oral treatment phase of staphylococcal PJI (the RiCOTTA study).

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, level of evidence: moderate

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.[46] 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.[46] 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.

5 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
10 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 leads to similar clinical outcomes as rifampicin with fluoroquinolones.
The RCT is likely to have been underpowered to demonstrate a difference. Four retrospective
15 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. We
chose to lower the evidence to moderate. The strength of the recommendation is conditional.

20 **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:

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

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

Rationale:

30 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).[47] 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 studies of sufficient
35 sample size.

A randomised controlled trial 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).[48] One systematic review only
40 contained the Byren study.[49]

Summary of evidence:

45 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.

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Streptococci

PICO 2a: In a person with a PJI caused by streptococci, is a rifampicin-based regimen more effective in achieving clinical cure?

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Recommendation:

We suggest not to use rifampicin for streptococcal PJI.

Strength of recommendation: conditional, level of evidence: low

10 **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 (mostly oral) streptococci.

15

In twenty-five studies, the outcome of acute streptococcal PJI treated with DAIR was reported. 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.[50] In this study, no antimicrobial therapy, alone or in combination, was associated with a better outcome. A trend towards a better prognosis in rifampicin–levofloxacin combinations was shown in the study by Fiaux et al., but this effect disappeared in the multivariate analysis.[51] 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).[52] The largest study on streptococcal PJIs also failed to show a benefit of rifampicin therapy.[53] 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.

30

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.[52] All studies were retrospective observational studies and were inherently hampered by selection bias, immortal time bias and confounding by indication.

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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.

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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.[50] However, in another study, virulent streptococci were not associated with a worse outcome.[53] In all other studies, outcome was not stratified for low-virulent or high-virulent streptococci.

45

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.

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Summary of evidence:

Four retrospective observational studies were identified that studied 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. However, there did not seem to be large inconsistencies, impreciseness or indirectness in the studies. 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.

10 **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.

15 **Strength of recommendation: conditional, level 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.[53] In one smaller study [54], amoxicillin was always combined with a second antibiotic. In the study by Fiaux et al.,[51] 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.

45 ***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?

50 **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, level of evidence: low

- 5 **Recommendation:**
We suggest to treat patients with amoxicillin-resistant enterococcal PJI with vancomycin monotherapy
Strength of recommendation: conditional, level of evidence: low

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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,[55-58] while another study reports superior results using combination treatment.[59] 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.[57, 60, 61]

20 *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.

25 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 level 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.[62] 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.[56] 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

- 50 **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.

5 **Strength of recommendation: strong, level of evidence: moderate**

Rationale:

10 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.[63-65] 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.[66] The success rate of patients treated with ciprofloxacin in ciprofloxacin-susceptible strains was 79% compared with 40% when patients were treated with other antibiotics (P 0.001), and the use of ciprofloxacin was an independent predictor of treatment success in the total cohort (aHR 0.23, 95% CI 0.13 – 0.40). Another smaller study (n=47) confirmed better outcomes of patients treated with ciprofloxacin compared to those treated with other antibiotics.[67] In addition, observational studies report excellent outcomes when a fluoroquinolone is part of the antibiotic regimen.[68, 69] 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.[70] 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:

30 Outcomes with fluoroquinolones were better than those with trimethoprim-sulfamethoxazole in pre-clinical and retrospective clinical studies. The effect was large in most studies. There was no large inconsistency or impreciseness or indirectness. The quality of evidence was moderate. Given the large effect on outcome and the consistency with pre-clinical studies, the relatively low rates of side effects of quinolones, the recommendation is strong.

35 ***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?

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Recommendation:

We suggest to treat *Cutibacterium acnes* PJI with amoxicillin.

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

45 *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

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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.[71]

Summary of evidence:

5 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, 10 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 15 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.

20 **PICO 5b: In a person with a PJI caused by *Cutibacterium (Propionibacterium) acnes*, is a rifampicin-based regimen more effective in achieving clinical cure?**

Recommendation:

We suggest not to treat *Cutibacterium acnes* PJI with a rifampicin-based regimen.

Strength of recommendation: conditional, level of evidence: low

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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.[72] The addition of rifampicin has been shown to improve cure rates of biofilms formed by *Cutibacterium 30 acnes* in vitro and in an animal foreign-body infection model.[73] 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.

35 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. [74, 75] 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.[76] However, 40 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:

45 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 level of evidence from moderate to low given the suboptimal design of the studies. Given the low level of 50 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

5 **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:

10 **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.**

Strength of recommendation: conditional, level of evidence: low

15 **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 6 weeks between operations is considered the optimal treatment with a success rate of 93%.[10, 77, 78]
20 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 higher than for anidulafungin while no data are available for caspofungin or micafungin.[79]

Studies:

30 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.[80] 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.

40 Koutserimpas et al.,[81] 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%.

50 *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:

5 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 higher drug levels in joint and bone tissue. 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 level of evidence is lowered from moderate to low given the high chance of bias in the studies.

Culture-negative

20 **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:

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

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

Recommendation:

30 **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, level of evidence: very low

Rationale:

35 Of the patients with PJI, 0-42% is culture negative (CN).[82] Prior antibiotic use is associated with CN PJI.[83, 84] 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.[82] Since no microorganism can be targeted with antibiotics, 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
40 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.[82, 85] In only one study,[86] the majority of
45 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
50 small study population and the retrospective nature of this study. In a retrospective cohort study,[83] 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 as this might increase the risk of bacterial resistance. 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.[87] 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.

10 *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).

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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.

45 **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, level of evidence: very low

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Recommendation:

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

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

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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.[88] 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.

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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.

25

7. Duration of therapy, route of administration and dosages

The Infectious Diseases Society of America (IDSA) guidelines recommends a 6-week course of intravenous antimicrobial therapy following resection arthroplasty for PJIs.[3] The treatment can be continued with oral antibiotics for another 3 months in case of staphylococcal total hip arthroplasty treated with 1SR and DAIR, and in case of knee replacement for 6 months. The consensus document does not give any 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.[89, 90] 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;[91] 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 bacteria in biofilm, 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. The group did not reach consensus on the recommendations for dosing. We recommended the minimal dose in the tables of recommendation, but the use of the highest possible dose of antibiotics is justifiable and common practice in certain centres in the Netherlands. More data are needed to come to specific recommendations on the exact doses of antibiotics in PJI.

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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?

5 ***Recommendation:***

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

10 ***Rationale:***

We found 6 articles that studied the effect of the length of antibiotic courses on treatment outcomes in subjects with PJI who underwent DAIR. All but one study found no inferior outcomes in patients with PJI who underwent DAIR treated for 6 to 8 weeks of antibiotics, compared with patients that received 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).[92] 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.[93] 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.[94] 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.[95]

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.[96] 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.[96]

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.[97] 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.[98]

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 challenged this view and showed that 6 weeks of antibiotic treatment in DAIR was inferior to 12 weeks (31% versus 15% failure rate, respectively) for various pathogens.[99] 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. 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.[100] This study, however, is prone to bias due to its study type and small study population.

Summary of evidence:

Some studies found no difference in outcome between 6 and 12 weeks of antibiotic treatment for DAIR. Since the studies compared 6 to 12 weeks, there is no rationale to treat for longer than 12 weeks. The large DATIPO study,[99] however, showed that outcomes after 12 weeks of treatment were superior to 6 weeks of antibiotics. Although there was some inconsistency, the level 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 think that the decision on the duration of antimicrobial therapy should also take into account the patients' personal circumstances (e.g., host characteristics and (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 acute PJI who undergo 1SR for 6 weeks, but the duration can be lengthened to 12 weeks depending on clinical circumstances.

Strength of recommendation: conditional, level 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).[101] 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.[95] 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.[102] 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.[96] But, this review included only one study (the study from Bernard et al.[95]) 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.[99]

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 level 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. The recommendation is

conditional. Although most studies examined 1SR, we also think that the same duration can be used in patients undergoing 2SR.

5

8. Timing of therapy

10 **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, level of evidence: very low.

15

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,[103] 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; $\chi^2=5.4$, 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.[104] 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 level 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. The lack of high level evidence leads to a conditional recommendation.

50

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?

5 ***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, level of evidence: very low.

10

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

15 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.[105]

20 After finishing the search strategy for this SWAB guideline, an observational study performed by

Beldman et al. was published.[106] 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). This study additionally supports the importance of adequate bacterial load reduction

25 prior to the start of rifampicin, but does not support waiting until the wound has stopped draining.

Summary of evidence:

The level of evidence is low (based on two observational studies). Since rifampicin is always given

with a second drug and usually intravenously, it is unlikely that low levels of antibiotics will lead to

30 rifampicin resistance after adequate surgical debridement has been performed.

35

Appendices

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

5 Appendix B: Bias Assessment

Appendix C: Evidence Tables

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

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

1. Culture directed antimicrobial therapy

20 *Staphylococci*

PICO 1a:

P *Staphylococcus* PJI
I rifampicin-based antibiotic regimen
C non-rifampicin-based antibiotic regimen
25 O cure

PICO 1b:

P *Staphylococcus* PJI
I non-fluoroquinolone combined with rifampicin
30 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 Initial IV treatment with monotherapy
- C Initial 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

5

PICO 6:

P *Candida* PJI

I 2 weeks initial IV treatment with fluconazole therapy

C 2 weeks initial IV treatment with other therapy

10 O cure

15 **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

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Culture-negative

PICO 7:

P: Culture-negative PJI

25 I: fluoroquinolone combined with rifampicin

C: other antibiotic regimen

O: Cure

30 **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:

35 Hits Pubmed: 147

Hits Embase: 179

Hits Coch/Clin: 4

2. Suppressive therapy

40

PICO 8:

P Suppressive AB for incurable PJI

I <2y of suppressive AB

C >2y of suppressive AB

45 O Need for surgical reintervention

50 **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

5 Hits Coch/Clin: 1

3. Duration of therapy

PICO 9a:

10 P: Acute PJIs treated with DAIR
I: 6 or 8 weeks of antibiotic treatment
C: 12 weeks of antibiotics treatment
O: Cure

15 **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

20

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])

25

Hits per database:

30 Hits Pubmed: 63

Hits Embase: 632

4. Timing of therapy

35 **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

40

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])

45

Hits per database:

50 Hits Pubmed: 8

Hits Embase: 36

PICO 11:

P: Acute staphylococcal PJI treated with DAIR

I: Immediate start of rifampicin after surgical debridement

5 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

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

Total hits 184

30 Staph 93

Strep 8

Enterococ 7

Enterobac 8

Cacnes 21

Candida 7

35 Culture Negative 12

Suppressive 10

Duration 5

Holiday 2

40 Timing 11

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2 Appendix B: Bias Assessment

3 **Table 1:** Risk of bias of included publications 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 | + | - | + | + | + | + | + | + | 7/8 |
| Ascione et al. 2017 | + | - | + | + | + | + | + | + | 7/8 |
| Aydın et al. 2020 | - | - | - | + | - | + | + | - | 3/8 |
| Becker et al. 2020 | + | - | + | + | - | - | - | - | 3/8 |
| Drancourt et al. 1997 | - | - | - | + | - | + | + | - | 3/8 |
| Holmberg et al. 2015 | + | - | + | - | - | + | + | - | 4/8 |
| Karlsen et al. 2020 | + | + | + | + | + | + | + | + | 8/8 |

| | | | | | | | | | |
|-------------------------|---|---|---|---|---|---|---|---|-----|
| Lesens et al. 2018 | + | - | + | + | - | + | + | - | 5/8 |
| Lora-Tamayo et al. 2012 | - | - | + | + | - | - | - | + | 3/8 |
| Senneville et al. 2011 | + | - | + | - | - | + | + | + | 5/8 |
| Tornero et al. 2016 | - | - | + | + | - | + | - | - | 3/8 |

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PICO 1c: no studies were included

Table 2a: Risk of bias of included publications for PICO 2a

| 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 | + | + | + | + | - | ? | ? | + | 5/8 |
| Fiaux et al. 2016 | + | - | + | + | - | ? | ? | - | 3/8 |

| | | | | | | | | | |
|-------------------------------|---|---|---|---|---|---|---|---|-----|
| Aydin et al. 2020 | + | - | + | + | - | ? | ? | - | 3/8 |
| Mahieux et al. 2019 | + | - | + | + | - | ? | ? | - | 3/8 |
| Wouthuyzen-Bakker et al. 2019 | + | - | + | + | - | + | + | - | 5/8 |

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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 | + | + | - | + | ? | + | + | + | 6/8 |
| Kheir et al. 2017 | + | + | - | + | ? | + | + | - | 5/8 |
| Thompson et al. 2019 | + | - | + | + | ? | + | + | + | 6/8 |
| Renz et al. 2019 | + | + | - | + | ? | + | + | - | 5/8 |

El Helou et al.
2008

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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 | + | + | - | + | ? | + | + | + | 6/8 |
| Martínez-Pastor et al. 2009 | + | ? | - | - | ? | + | + | - | 3/8 |
| Grossi et al. 2016 | + | - | + | + | ? | + | + | ? | 5/8 |

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PICO 5a: no studies were included

Table 5a: Risk of bias of included cohort 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 | + | - | + | + | - | + | - | - | 4/8 |
| Jacobs et al. 2015 | + | - | + | + | - | + | + | - | 5/8 |
| Kusejko et al. 2021 | + | - | + | + | - | + | + | - | 5/8 |

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

| Reference | | Aydin et al. 2020 |
|-------------------------------------|--|-------------------|
| Section 1: Internal validity | | |
| 1.1 | The research question is clearly defined and the inclusion/exclusion criteria must be listed in the paper. | + |
| 1.2 | A comprehensive literature search is carried out. | + |

| | | |
|----------|---|---|
| 1.3 | At least two people should have selected studies. | + |
| 1.4 | At least two people should have extracted data. | + |
| 1.5 | The status of publication was not used as an inclusion criterion. | + |
| 1.6 | The excluded studies are listed. | - |
| 1.7 | The relevant characteristics of the included studies are provided. | + |
| 1.8 | The scientific quality of the included studies was assessed and reported. | + |
| 1.9 | Was the scientific quality of the included studies used appropriately? | + |
| 1.1 0 | Appropriate methods are used to combine the individual study findings. | + |
| 1.1 1 | The likelihood of publication bias was assessed appropriately. | + |
| 1.1 2 | 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 <i>Cutibacterium acnes</i>) is applicable to this PICO-question. | |

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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 | + | - | + | + | - | + | - | - | 4/8 |
| Koutserimpas et al. 2019 | + | - | + | + | - | + | + | - | 5/8 |

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Table 7a: Risk of bias of included cohort 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 | + | - | + | - | - | + | + | - | 4/8 |
| Choi et al. 2012 | + | - | + | + | - | + | - | - | 4/8 |
| Huang et al. 2012 | + | - | + | + | - | + | - | - | 4/8 |
| Ibrahim et al. 2018 | + | + | + | + | - | + | - | - | 5/8 |
| Wang et al. 2018 | + | - | + | - | - | + | - | + | 3/8 |
| Santoso et al. 2018 | + | - | + | - | - | + | - | - | 3/8 |

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

| Reference | | Yoon et al. 2017 | Reisener & Perka 2018 |
|-------------------------------------|--|------------------|-----------------------|
| Section 1: Internal validity | | | |
| 1.1 | The research question is clearly defined and the inclusion/exclusion criteria must be listed in the paper. | + | + |
| 1.2 | A comprehensive literature search is carried out. | + | + |
| 1.3 | At least two people should have selected studies. | + | + |
| 1.4 | At least two people should have extracted data. | + | ? |
| 1.5 | The status of publication was not used as an inclusion criterion. | - | ? |
| 1.6 | The excluded studies are listed. | - | - |
| 1.7 | The relevant characteristics of the included studies are provided. | + | + |
| 1.8 | The scientific quality of the included studies was assessed and reported. | - | +/- |

| | | | |
|---|--|---|-----|
| 1.9 | Was the scientific quality of the included studies used appropriately? | - | +/- |
| 1.1 0 | Appropriate methods are used to combine the individual study findings. | - | + |
| 1.1 1 | The likelihood of publication bias was assessed appropriately. | - | + |
| 1.1 2 | 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. | | |

1 **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 | + | - | +/- | + | - | + | - | + | |
| Leijtens et al. 2019 | | | | | | | | | |
| Pavoni et al. 2004 | | | | | | | | | |
| Prendki et al. 2017 | | | | | | | | | |
| Pradier et al. 2018 | | | | | | | | | |
| Prendki et al. 2014 | | | | | | | | | |
| Rao et al. 2003 | | | | | | | | | |
| Sandiford et al. 2019 | | | | | | | | | |

Wouthuyzen-
Bakker et al.
2017

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Table 8b: Risk of bias of the included meta-analysis for PICO 5b

| Reference | | Malahias et al. 2019 |
|-------------------------------------|--|-------------------------|
| Section 1: Internal validity | | |
| 1.1 | The research question is clearly defined and the inclusion/exclusion criteria must be listed in the paper. | + |
| 1.2 | A comprehensive literature search is carried out. | + |
| 1.3 | At least two people should have selected studies. | + |
| 1.4 | At least two people should have extracted data. | ? |
| 1.5 | The status of publication was not used as an inclusion criterion. | ? |
| 1.6 | The excluded studies are listed. | - |

| | | |
|----------|--|-----|
| 1.7 | The relevant characteristics of the included studies are provided. | + |
| 1.8 | The scientific quality of the included studies was assessed and reported. | + |
| 1.9 | Was the scientific quality of the included studies used appropriately? | + |
| 1.1 0 | Appropriate methods are used to combine the individual study findings. | +/- |
| 1.1 1 | The likelihood of publication bias was assessed appropriately. | - |
| 1.1 2 | 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 | |

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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 | + | - | + | + | - | + | - | - | 4/8 |
| Ma et al. 2019 | + | - | + | + | - | ? | - | - | 3/8 |
| Hsieh et al. 2009 | + | - | + | + | - | + | - | - | 4/8 |
| El Helou et al. 2011 | + | - | + | + | - | ? | - | + | 4/8 |
| Chaussade et al. 2017 | + | - | + | + | - | + | - | + | 5/8 |
| Bernard et al. 2010 | + | + | + | + | - | ? | - | + | 5/8 |

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

| Reference | | Yen et al. 2019 |
|-------------------------------------|--|-----------------|
| Section 1: Internal validity | | |
| 1.1 | The research question is clearly defined and the inclusion/exclusion criteria must be listed in the paper. | + |
| 1.2 | A comprehensive literature search is carried out. | + |
| 1.3 | At least two people should have selected studies. | + |

| | | |
|---|---|---|
| 1.4 | At least two people should have extracted data. | ? |
| 1.5 | The status of publication was not used as an inclusion criterion. | + |
| 1.6 | The excluded studies are listed. | - |
| 1.7 | The relevant characteristics of the included studies are provided. | + |
| 1.8 | The scientific quality of the included studies was assessed and reported. | + |
| 1.9 | Was the scientific quality of the included studies used appropriately? | + |
| 1.1 0 | Appropriate methods are used to combine the individual study findings. | + |
| 1.1 1 | The likelihood of publication bias was assessed appropriately. | + |
| 1.1 2 | 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: | |

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

| Item | Benkabouche et al. 2019 | Lora-Tamayo et al. 2016 |
|--|-------------------------|-------------------------|
| 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? | + | + |

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1 **Appendix C: Evidence Tables**

2 **Table 1a:** Evidence Table for PICO 1a and PICO 1b (*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 level of evidence & Risk of Bias | Comments |
|---------------------|---|--|---|---|---|---|---|
| Ascione et al. 2015 | 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%) $\chi^2 = 10.9$, RR 1.6, 95% CI 1.17-2.23; $p = 0.0001$. | SIGN level 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; $\chi^2 = 10.9$, 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

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 level
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)

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| | | | | | | |
|--------------------------|---|---|--|--|--|--|
| <p>Aydın et al. 2020</p> | <p>Study design Meta-analysis</p> <p>Setting: Inpatient</p> <p>Follow up: Median .. weeks</p> | <p>Subjects (n): total 568, 360 SA, 196 CNS</p> <p>I: n=68+22+69+44+23+31+38+60 = 325</p> <p>C: n=30+17+12+41+16+56+14+27 = 211</p> <p>Type of surgery: DAIR hip knee (Senneville also 1SR/2SR/resection/arthrodesis. Ascione: not DAIR, only 2-stage</p> | <p>I: Rifampicin remission</p> <p>C: No rifampicin</p> | <p>Outcome 1: (SA+CNS)</p> <p>I: 256 (cure rate 79%)</p> <p>C: 148 (cure rate 70%)</p> <p>58+14+56+41+4+21+24+41 = 256</p> <p>19+14+8+39+5+35+9+19 = 148</p> <p>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]).</p> | <p>SIGN level of evidence: 1-</p> <p>Risk of bias: 3/8</p> | <p>8 observational studies on SA (4 good, 2 fair, 2 poor quality)</p> <p>568 (360 SA, 196 CNS)</p> <p>Senneville SA 58/68 rifa succ, 19/30 no rifa succ.</p> <p>Morata: remisson SA 8/9 89% (6 rifa, remission % n.r.), remission CNS 19/33 56% (18 rifa, remission% n.r.)</p> <p>Aydın: all pathogens combined: remission 64% 14/22 rifa+, 82%14/17 rifa-).</p> <p>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</p> <p>Ascione 2017: 85 staph, (44 SA, 41 CNS), rifa + 41/44 (93% success), rifa - 39/41 (95% success) (S aureus/CNS not specified)</p> <p>Soriano rifa+ 4/23 rifa- 5/16</p> <p>El Helou rifa+ 21/31, rifa- 35/56</p> <p>Puhto rifa+ 24/38, rifa- 9/14</p> <p>Chaussade rifa+ 41/60, rifa- 19/27</p> |
|--------------------------|---|---|--|--|--|--|

Becker et al.
2020

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

Holmberg et al. 2015

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 level 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

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 level of evidence: 2++

Risk of bias: 8/8

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)

CONCEPT

Lesens et al.
2018

Retrospective cohort,
multicentre

subjects (n):
I: n=89 rifa (63 rifa +FQ)
C: n=48 no rifa (26 rifa -FQ)

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 level
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.

Setting:
Inpatient

Mean age (years):
All 137 subjects: 73 ± 13 years;
I: n.r.
C: n.r.

Follow up:
24 months

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

CONCEPT

| | | | | | | | |
|-------------------------|---|--|---|--------------------------------|--|--|--|
| Lora-Tamayo et al. 2013 | <p>Study design retrospective, multicentre, observational study</p> <p>Setting: Inpatient</p> <p>Follow up: Not specified (>28 months)</p> | <p>subjects (n):total 345 I: n=303 rifa C: n=42 (?)</p> <p>Mean age (years): All subjects 73 (27-95) I: n.r. C: n.r.</p> <p>Male sex: All subjects: 41% I: n.r. C: n.r.</p> <p>Lost to follow up (n): Total 17 (5%) (volgens Kaplan Meier 174 (54%)?) I: n.r. C: n.r.</p> <p>Type of surgery: DAIR. Hip/knee/other</p> | <p>I: Rifampicin C: No rifampicin</p> | <p>In remission vs failure</p> | <p>Outcome 1: I: n.r. C: n.r.</p> <p>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.</p> <p>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</p> | <p>SIGN level of evidence: 2-</p> <p>Risk of bias: 3/8</p> | <p>No specific numbers on I/C, only HR</p> |
|-------------------------|---|--|---|--------------------------------|--|--|--|

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

CONCEPT

Tornero et al. 2016

Study design
Retrospective analysis on prospective cohort

subjects (n): total Gram pos 89 of which 53 S aureus
I: n=78 rifa
C: n=11

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%)

SIGN level of evidence: 2-

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%).

Setting:
Inpatient

Mean age (years):
All subjects: 71.9 (+/- 10.1) years

No relapse
I: 74 (no relapse rate 95%)
C: 11 (no relapse rate 100%)

Risk of bias: 3/8

Follow up:
n.r. (min >2 years after +/- 11 wks treatment)

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

-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.

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PICO 1c: no studies were included

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

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

CONCEPT

| | | | | | | | |
|-------------------|---------------------|--|---------------------------------------|--|--|---|--|
| Fiaux et al. 2016 | Cohort study | Subjects: n=95 I: n=52 C: n=43 | 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 level 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. |
| | Setting: inpatient | Mean age in years: 69 | | | | | |
| | Follow up: >2 years | 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 | | | | | |

| | | | | | | | |
|-------------------|-------------------------------------|--|---------------------------------------|--|---|---|---|
| Aydın et al. 2020 | Systematic review and Meta-analysis | subjects (n): 483 I: n=191 C: n=292 Setting: Mean age (years) I: not stated C: not stated Follow up: 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 level of evidence: 2+ Risk of bias: 3/8 | This sys review includes 3 streptococcal PJI studies (Fiaux, Mahieu, Lora-Tamayo) |
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| Lora-Tamayo et al. 2017 | 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 level of evidence: 2+ Risk of bias: 5/8 |
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| Mahieux et al. 2019 | Cohort study | subjects (n): 70 I: n=31 | I: 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 level 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) |
| | Setting: inpatient | C: n=39 | C: No rifampicin | | | | |
| | Follow up:>2years | 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: | | | | | |

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

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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 level of evidence & Risk of Bias | Comments |
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| <p>Tornero et al. 2014</p> | <p>Retrospective Setting: multicentre 18 hospitals Follow up: Med 722 days (range 168 – 1529)</p> | <p>subjects (n): I: n=127 C: n=51 Lost to follow up (n): 0 Type of surgery: DAIR, revision surgery.</p> | <p>I: Combination therapy. C: Monotherapy.</p> | <p>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.</p> | <p>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:</p> | <p>SIGN level of evidence: 2- Risk of bias: 5/8</p> | <p>The duration of combination therapy was not defined. Additional agents for combination treatment: aminoglycoside or rifampicin</p> |
| <p>Kheir et al. 2017</p> | <p>Retrospective Setting: 3 institutions Follow up: Range 1 – 12 years.</p> | <p>subjects (n): 87 I: not specified C: not specified Lost to follow up (n): 0 Type of surgery: DAIR, revision surgery.</p> | <p>I: Combination therapy. C: Monotherapy.</p> | <p>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.</p> | <p>Treatment success: I versus C: P = 0.174, results not specified.</p> | <p>SIGN level of evidence: 2- Risk of bias: 6/8</p> | <p>The duration of combination therapy was not defined. Additional agents for combination treatment not specified.</p> |

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| Thompson et al. 2019 | 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 level of evidence: 2- | Additional agents for combination treatment: rifampicin for > 2 weeks (range 19 – 200 days) |
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| <p>Renz et al. 2019</p> | <p>Retrospective Setting: 2 large orthopaedic hospitals Follow up: Med 31.8 months (range 0.3 – 83.3)</p> | <p>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</p> | <p>I: Combination therapy. C: Monotherapy.</p> | <p>Treatment success - defined as the absence of relapse or persistence of PJI due to enterococci or death related to enterococcal PJI</p> | <p>Treatment success: I: 73% C: 88% P=0.217</p> | <p>SIGN level of evidence: 2- Risk of bias: 5/8</p> | <p>Additional agents for combination therapy: Fosfomycin, gentamicin, vancomycin or daptomycin. The duration of IV combination therapy was not defined.</p> |
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| <p>El Helou et al. 2008</p> | <p>Retrospective cohort study</p> <p>Setting: single-centre</p> <p>Median follow up in days (range): 1253 (29-4610)</p> | <p>Episodes: n=50 (in n=47 subjects) I: n=19 C: n=31</p> <p>Median age in years (range): 70 (32-89)</p> <p>Male sex: n=25 (50%)</p> <p>TKP: n=24 (48%) THP: n=26 (52%)</p> <p>Type of surgery: n=17 (34%) 2SR n=4 (8%) 1SR n=5 (10%) DAIR n=1 (2%) amputation n=23 (46%) resection arthroplasty</p> | <p>I: Combination therapy</p> <p>C: Monotherapy</p> | <p>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.</p> <p>Cranial nerve VIII toxicity</p> <p>Nephrotoxicity</p> | <p>Treatment failure I: n=7 (37%) C: n=5 (16%) P=0.2</p> <p>Cranial nerve VIII toxicity I: n=6 (32%) C: n=0 (0%) P=0.002</p> <p>Nephrotoxicity I: n=5 (26%) C: n=2 (6%) P=0.09</p> | <p>SIGN level of evidence: 2-</p> <p>Risk of bias:</p> | <p>Additive agents for combination therapy: aminoglycoside</p> |
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1 **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 level of evidence & Risk of Bias | Comments |
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| Rodríguez-Pardo et al. 2014 | 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 level 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. |

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

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2 **PICO 5a:** no studies were included
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4 **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 level of evidence & Risk of Bias | Comments |
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| Piggott et al. 2015 | Retrospective cohort study | Subjects: n=21 I: n=15 (71.4%) C: n=6 (28.5%) | 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. | Favourable: I: n=11/15 (73%) C: n=3/5 (60%) P=0.61 | SIGN level 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 <i>C acnes</i> PJIs requires further study. |
| | Setting: single-centre | Type of PJI n=21 (100%) shoulder | | | | | <u>Rifampicin doses:</u> not mentioned. |
| | Median follow-up in months: 24 | 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 | | The final clinical outcome was determined as per the clinical status at the last recorded clinical visit. | | | <u>Side-effects of rifampicin:</u> n=6 (40%) stopped using rifampicin due to side-effects. |
| | | Median age in years (range): 62 (40-81) I: not stated C: not stated | | | | | <u>Antibiotic combinations:</u> not mentioned. |
| | | Male sex: n=19 I: not stated C: not stated | | | | | |
| | | LTFU: n=1 (4.8%) I: n=0 C: n=1 (17%) | | | | | |

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| Aydın et al. 2021 | <p>Meta-analysis</p> <p>Setting: 2 single-centre observational studies (Piggott et al.2015 & Jacobs et al. 2015)</p> <p>Follow-up time: not stated</p> | <p>Subjects: n=80 I: n=54 (67.8%) C: n=26 (32.5%)</p> <p>Type of PJI: Shoulder, knee, hip</p> <p>Type of surgery: - DAIR - Replacement surgery (numbers not stated) Mean/median age (years): not stated</p> <p>Male sex: I: not stated C: not stated</p> <p>LTFU: not stated</p> | <p>I: Rifampicin</p> <p>C: No rifampicin</p> | <p>Failure - defined as death or relapse or recurrence of PJI.</p> | <p>Failure: I: n=8 (14.8%) C: n=5 (19.2%) RR 1.61 (0.58-4.47)</p> | <p>SIGN level of evidence: 1+</p> <p>Risk of bias: 13/14</p> | <p>NB: This systematic review includes the studies from Jacobs et al. and Piggott et al.</p> <p><u>Conclusion:</u> In the <i>C acnes</i> subsets, neither individual nor combined analysis favoured rifampicin-based regimens.</p> <p><u>Rifampicin doses:</u> not mentioned.</p> <p><u>Side-effects of rifampicin:</u> not mentioned</p> <p><u>Antibiotic combinations:</u> not mentioned.</p> |
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| <p>Jacobs et al. 2015</p> | <p>Retrospective cohort study</p> <p>Setting: Single-centre</p> <p>Follow-up: 1 year and 2 years</p> | <p>Subjects: n=60 I: n=39 C: n=21</p> <p>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</p> <p>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</p> <p>Median age in years (range): 69 (40, 80) I: 69 (40, 78) C: 69 (47, 80)</p> <p>Male sex: 31 (51.7%) I: n=17 (43.6%) C: n=14 (66.7%)</p> <p>LTFU: - 1 year follow-up: n=0 (0%) - 2 years follow-up: n=24 (40%)</p> | <p>I: Rifampicin C: No rifampicin</p> | <p>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.</p> <p>A relapse was defined as positive cultures yielding the same microorganism as the initial intraoperative samples.</p> <p>A reinfection was defined as a new infection with another pathogen.</p> | <p>Failure <i>After 1 year</i> I: n=2/39 (5.1%) C: n=2/21 (9.5%) <i>P=0.7</i></p> <p><i>After 2 years</i> I: n=4/23 (17.4%) C: n=3/13 (23.1%) <i>P=0.6</i></p> <p>Relapse <i>After 2 years</i> I: n=2 (5.1%) C: n=2 (9.5%) <i>P=0.4</i></p> <p>Reinfection <i>After 2 years</i> I: n=2 (5.1%) C: n=1 (4.8%) <i>P=0.5</i></p> | <p>SIGN level of evidence: 2+</p> <p>Risk of bias: 5/8</p> | <p><u>Conclusion:</u> <i>C acnes</i>-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.</p> <p><u>Rifampicin doses:</u> 450 mg 2x/day</p> <p><u>Side-effects of rifampicin:</u> No (0%) subjects stopped using rifampicin due to side-effects.</p> <p><u>Antibiotic combinations:</u> 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).</p> |
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| Kusejko et al. 2021 | Retrospective cohort study | Subjects: n=187 I: n=81 C: n=106 | I: Rifampicin C: No rifampicin | Treatment failure - defined as either infection relapse, new infection, or death from PJI. | Overall Failure I: n=10 (12.3%) C: n=28 (26.5%) P=0.0288 | SIGN level of evidence: 2+ Risk of bias: 5/8 | <u>Conclusion:</u> When adjusting for surgical strategy and overall duration of antibiotic treatment, the effect of adding rifampicin was <u>not</u> 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. |
| | Setting: Multicentre (9 countries, 18 centres) | Type of PJI: I: - n=40 (49.4%) Hip - n=34 (42.0%) Shoulder | | 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 | Relapse proven and possible I: n=8 (9.9%) C: n=20 (18.9%) P=0.1334 | | <u>Rifampicin doses:</u> - 44.4% 450 mg 2x/day - 27.8% 600 mg 1x/day - 33.3% no doses recorded |
| | Median follow-up in months (IQR): 36 (23-60) | Shoulder - n=7 (8.6%) Knee - n=0 (0.0%) Other C: - n=57 (53.4%) Hip - n=36 (34.0%) Shoulder | | <i>C. acnes</i> . Defined as possible when not microbiologically proven but suggested by persisting symptoms or signs of infection. | New Infection I: n=2 (2.5%) C: n=11 (10.4%) P=0.0692 | | <u>Side-effects of rifampicin:</u> not mentioned |
| | | Shoulder - n=10 (9.43%) Knee - n=3 (2.8%) Other | | New infection - defined as a microbiologically proven infection in case of a new pathogen detected in ≥ 2 diagnostic samples during the follow-up period. | 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 | | <u>Antibiotic combinations:</u> 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). |
| | | 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 | | | | | |



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%)

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

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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 level of evidence & Risk of Bias | Comments |
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| Kim et al. 2015 | <p>Systematic review</p> <p>Setting: 20 articles included</p> <p>Mean follow up time in months: 34</p> | <p>Subjects n=37 I: n=6 C: n=9</p> <p>Mean age in years: 65</p> <p>Male sex: 16 (43%)</p> <p>Lost to follow up: not mentioned</p> <p>Type of surgery: Removal of the prosthesis n=32 (87%) DAIR n=2 None n=3</p> <p>Type of joint: Hip n=37 (100%)</p> | <p>Sub analysis: I: THA reimplantation with antifungals impregnated cement spacer C: THA reimplantation without (impregnated) cement spacer</p> | <p>Relapse rate of <i>Candida</i> spp. infection</p> | <p>Relapse rate of <i>Candida</i> spp. infection I: n=0 (0%) C: n= 1 (11%) P=0.606; OR: 0.889 95%CI: 0.168-4.701</p> | <p>SIGN level of evidence: Risk of bias: 4/8</p> | <p>hypothesis was that staged reimplantation of a total hip prosthesis after <i>Candida</i> spp. infection is a reliable procedure providing symptomatic relief and successful outcomes.</p> <p>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</p> <p>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.</p> <p>Since echinocandin has significant fungicidal activity against <i>Candida</i> spp. with favourable safety</p> |
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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.

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| <p>Koutserimpas et al. 2019</p> | <p>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)</p> | <p>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%)</p> | <p>Sub analysis: I: 2SR C: 1SR</p> | <p>Success rate - not defined</p> | <p>Success rate I: 96% C: 73% P=0.023</p> | <p>SIGN level of evidence: Risk of bias: 5/8</p> | <p><i>C.parapsilosis</i> is the predominant pathogen. MIC's for echinocandins are usually elevated and were not used. <i>C. glabrata</i> 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.</p> |
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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 level of evidence & Risk of Bias | Comments |
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| Tirumala et al. 2020 | 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 level 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 |
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| Choi et al. 2012 | Retrospective cohort study | Subjects: n=175 I: n=40 C: n=135 | I: culture negative | Treatment success- defined as subjects who did not receive any additional surgical procedure for persistent or recurrent infection after initial surgical treatment | Treatment success I: n=34 (85%) C: n=83 (61%) | Risk of bias: 4/8 | Does not compare type of antibiotics used in culture negative group. |
| | Setting: single-centre | Type of PJI: I: | C: culture positive | | Treatment failure I: n=6 (15%) C: n=52 (39%) | SIGN level of evidence: 2- | 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. |
| | Mean follow-up time in months (range): 58 (24-26) | - n=20 hip (50%) - n=20 knee (50%) C: - n=77 hip (57%) - n=58 knee (43%) | | Treatment failure - defined as subjects who necessitated any additional surgical procedure for infection control. | P=0.006 | | <u>IV Antibiotics in intervention group:</u> - Vancomycin n=28 (70%) - Others n=12 (30%) |
| | | Type of surgery: n=56 DAIR n=110 2SR n=7 reimplantation n=2 arthrodesis | | | | | Includes around 60% of chronic PJI. |
| | | 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 | | | | | |

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| <p>Huang et al. 2012</p> | <p>Retrospective cohort study</p> <p>Setting: single-centre</p> <p>Mean follow-up time in months (range): I: 47 (12-119) C: 33.2 (12-125.7)</p> | <p>Subjects: n=343 I in 298 subjects I: n=48 I/subjects C: n=295 I in 250 subjects</p> <p>Type of PJI: I: - n=21 hip (38%) - n=28 knee (51%) C: Not mentioned</p> <p>Mean age in years (range): I: 63.7 (39-85) C: 66.7 (18-89)</p> <p>Male sex: I: 19 (40%) C: 122 (49%)</p> <p>Lost to follow up: n=25</p> <p>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 prostac</p> | <p>I: culture negative</p> <p>C: culture positive</p> | <p>Infection control - was defined as the preservation of the prosthesis in the index joint without any further surgery related to infection.</p> | <p>Infection control I: n=37 (73%) C: 73% P=1.00</p> <p>Survival Kaplan Meier shows similar infection-free survival between I and C after I&D (P=0.73) and 2SE (P=0.96)</p> <p>n=11 (28.2%) of I who were treated with vancomycin failed treatment.</p> | <p>Risk of bias: 4/8</p> <p>SIGN level of evidence: 2-</p> | <p>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.</p> <p><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</p> |
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| Ibrahim et al. 2018 | <p>Prospective cohort study</p> <p>Setting: single-centre</p> <p>Mean follow-up time in years: minimum 5 years</p> | <p>Subjects: n=100 I: n=50 C: n=50</p> <p>Type of PJI: n=100 (100%) hip</p> <p>Type of initial surgery: n=100 (100%) 2SR</p> <p>n=100 (100%) chronic infection</p> <p>Mean age in years (range): I: 74 (43-88) C: 71 (41-83)</p> <p>Male sex: I: 23 (%) C: 21 (%)</p> <p>Lost to follow up: n=8</p> | <p>I: culture negative</p> <p>C: culture positive</p> | <p>Re-infection</p> <p>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.</p> | <p>Re-infection I: n=3 (6%) C: n=3 (6%) P=0.19</p> | <p>Risk of bias: % SIGN level of evidence: 2+</p> | <p>Does not compare type of antibiotics used in culture negative group.</p> <p><u>IV Antibiotics in intervention group</u>: not mentioned</p> |
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| Reisener & Perka 2018 | Systematic review | Subjects: n=3342 I: n=504 C: n= | I: Culture negative | Incidence rate of culture negative PJI among subjects with PJI | Overall incidence rate estimate of culture negative PJI among subjects with PJI (95% CI): 11% (10-12) | Risk of bias: 7/14? | Does not compare outcomes between type of antibiotics used in culture negative group. |
| | 8 included studies Median follow-up time in months, range: 36-127.2 | 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 | C: Culture positive | Antibiotics used Successful treatment | 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% | SIGN level of evidence: 1- | Conclusion: vancomycin is used most often. It is unclear what the best treatment option is. |

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| <p>Santoso et al. 2018</p> | <p>Retrospective cohort study</p> <p>Mean follow-up time in months (range): I: 29.5 (12-78) C: 30.9 (12-71)</p> | <p>Subjects: n=84 I: n=27 C: n=57</p> <p>Type of PJI: n=84 (100%) hip</p> <p>Type of surgery: n=84 (100%) intended 2SR (n=6 followed different pathway in the end due to varying circumstances)</p> <p>Mean age in years (range): I: 67.4 (40-85) C: 67.3 (36-84)</p> <p>Male sex: I: 15 (55%) C: 30 (52.6%)</p> <p>LTFU: n=10</p> | <p>I: Culture negative</p> <p>C: Culture positive</p> | <p>Infection control - not defined</p> <p>Infection recurrence - not defined</p> | <p>Infection control I: n=25 (92.6%) C: n=47 (82.4%) P=0.21</p> <p>Infection recurrence I: n=2 (7.7%) C: n=8 (15.4%)</p> | <p>Risk of bias: 3/8</p> <p>SIGN level of evidence: 2-</p> | <p>Does not compare outcomes between type of antibiotics used in culture negative group within own study population.</p> <p>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.</p> <p><u>IV Antibiotics in intervention group:</u> n=23 (85.2%) cephalosporin n=8 (29.7%) vancomycin n=2 (7.4%) ciprofloxacin</p> |
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| Wang et al. 2018 | <p>Retrospective cohort study</p> <p>Setting: single-centre</p> <p>Median follow-up time in months (IQR): 68.5 (41-97.3)</p> | <p>Subjects: n=58 I: n=19 C: n=39</p> <p>Type of PJI: n=58 (100%) hip</p> <p>Type of surgery: n=58 (100%) intended 2SR (n=10 (17.2%) followed different pathway in the end due to varying circumstances)</p> <p>Mean age in years (range): 65.4 (36-86) I: 61 (50-75) C: 69 (60-76)</p> <p>Male sex: I: n=8 (42%) C: n=21 (54%)</p> <p>LTFU: n=0 (0%)</p> | <p>I: Culture negative</p> <p>C: Culture positive</p> | <p>Re-infection - not defined</p> | <p>Re-infection: n=4 (6.9%) I: n=0 (0%) C: n=4 (10.2%) P=0.397</p> <p>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</p> | <p>Risk of bias: 3/8</p> <p>SIGN level of evidence: 2-</p> | <p>Does not compare outcomes between type of antibiotics used in culture negative group.</p> <p><u>IV Antibiotics in intervention group:</u> I: rifampicin and levofloxacin.</p> |
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| <p>[1] Yoon et al. 2017</p> | <p>Systematic review</p> <p>7 included studies</p> <p>Mean follow-up time not mentioned</p> | <p>Subjects: n=495</p> <p>Type of PJI: hip and knee (numbers not mentioned)</p> <p>Type of surgery: 2SR, DAIR, 1SR, permanent resection</p> <p>Mean age in years: not mentioned</p> <p>Male sex: not mentioned</p> <p>Lost to follow up: not mentioned</p> | <p>No intervention/control group</p> <p>All subjects: culture negative PJI</p> | <p>Prevalence of culture negative PJI in subjects with PJI.</p> <p>Major risk factors for CN PJI</p> <p>Antibiotics used</p> | <p>Prevalence of culture negative PJI in subjects with PJI, range: 0%-42.1%</p> <p>Major risk factors for CN PJI:</p> <ul style="list-style-type: none"> - prior antibiotic use - presence of postoperative wound drainage. <p>IV Antibiotics, range:</p> <ul style="list-style-type: none"> - Glycopeptide 12-100% - Cephalosporins 10-82% - Other 6-30% | <p>Risk of bias: 6/14</p> <p>SIGN level of evidence: 1-</p> | <p>Does not compare outcomes between type of antibiotics used in culture negative group.</p> <p>No quality assessment of included studies; statements are rarely supported by numbers.</p> <p>Conclusion: further studies are needed to establish standard diagnostic methods for identifying infecting organisms and treatment strategies for CN PJI.</p> |
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1 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 =
2 intervention group; IQR = interquartile range; LTFU = lost to follow up; n = number; P = p-value; PJI = prosthetic joint infection
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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 level of evidence & Risk of Bias | Comments |
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| Escudero-Sanches et al. 2020 | <p>Retrospective case series with embedded case-control study</p> <p>Setting: Multicentre (29 hospitals)</p> <p>Follow-up in months: minimum 6 months</p> | <p>Subjects: n=302 Cases: n=125 (41.4%) Controls: n=177 (58.6%)</p> <p>Type of PJI: n=157 (52%) knee n=136 (45.0%) hip n=9 (3.0%) upper limb</p> <p>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</p> <p>Mean age in years (SD): Cases: 74.3 (13.9) Controls: 76.3 (13.9)</p> <p>Male sex: Cases: n=51 (41.8%) Controls: n=71 (58.2%)</p> <p>LTFU: n=<21</p> | <p>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.</p> <p>Controls: SAT success - cases in which none of the above described events occurred.</p> | <p>Age</p> <p>Type of microorganism</p> <p>Location of PJI</p> | <p>Median duration of SAT in months (IQR): 36.5 (20.75-59.21)</p> <p>Multivariate analyses; variables that are associated with SAT failure: - Age > 70 years <i>P</i>=0.013 - Other microorganism than gram-positive cocci <i>P</i>=0.025 -PJI in the upper limb. <i>P</i>=0.000</p> | <p>SIGN level of evidence:</p> <p>Risk of bias:</p> | <p>Among the possible causes for the failure of SAT, the reported causes were the suspension of SAT in 21/125 subjects (16.8%)</p> |
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| Leijtens et al. 2019 | 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 level of evidence: Risk of bias: |
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| <p>Malahias et al. 2019</p> | <p>Systematic review</p> <p>Included studies: 7</p> <p>Mean follow-up per study in years, range: 2.3-5</p> | <p>Subjects: n=424 (treated with SAT and DAIR)</p> <p>Type of PJI: hip, knee, elbow, shoulder</p> <p>Type of surgery: n=437 (100%) DAIR</p> <p>Male sex: 71.6%</p> <p>Mean age per study in years, range: 61.7-66 years</p> | <p>N/A</p> | <p>Infection free</p> <p>All-cause re-operation</p> <p>Adverse effects associated with long-term antibiotic use</p> | <p>Infection free n=318/424 (75%)</p> <p>All-cause re-operation: n=12/178 (6.7%)</p> <p>Adverse effects associated with long-term antibiotic use: n=29/188 (15.4%)</p> | <p>SIGN level of evidence:</p> <p>Risk of bias:</p> | <p><u>Conclusion:</u> 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.</p> |
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| Pavoni et al. 2004 | 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 level of evidence: 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. |
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| Pradier et al. 2018 | 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 level of evidence: Risk of bias: | Aim: to describe the use of oral cyclines as SAT in subjects with PJI |
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| Prendki et al. 2017 | Cross-sectional cohort study 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 level of evidence: Risk of bias: | Subjects >= 75 years |
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| Prendki et al. 2014 | 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 level of evidence: Risk of bias: | Subjects >=80 years |
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| <p>Rao et al. 2003</p> | <p>Prospective case series</p> <p>Setting: single centre</p> <p>Mean follow-up in months (range): 61.5 (16-128)</p> | <p>Subjects: n=36</p> <p>Type of PJI: n=15 (42%) hip n= 19 (53%) knee n=2 (5.5%) elbow</p> <p>Type of surgery: n=36 (100%) DAIR</p> <p>Mean age in years (range): 77 (62-96)</p> <p>Male sex: n=19 (53%)</p> <p>LTFU: not mentioned</p> <p>Mean duration of SAT treatment in months (range): 52.6 (6-128)</p> | <p>N/A</p> | <p>Treatment failure - defined as the development of progressive pain, loosening of the implant, or drainage despite antibiotic therapy.</p> <p>Complications related to antibiotic therapy</p> | <p>Treatment failure n=5 (14%)</p> <p>Duration of SAT (and number of treatment failures):</p> <ul style="list-style-type: none"> - 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) <p>→ All treatment failures happened while subjects were still using SAT.</p> <p>Complications related to antibiotic therapy: n=3 (8%)</p> | <p>SIGN level of evidence:</p> <p>Risk of bias:</p> | <p>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.</p> |
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| Sandiford et al. 2019 | 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 level of evidence: Risk of bias: | Conclusion: Prolonged suppressive antibiotic therapy is a viable option for the management of PJI with a low incidence of complications. |
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| <p>Wouthuyzen-Bakker et al. 2017</p> | <p>Retrospective case series</p> <p>Setting: Single centre</p> <p>Median follow-up in months (range): 21 (3-81)</p> | <p>Subjects: n=21</p> <p>Type of PJI: n=13 (62%) hip n=6 (29%) knee n=2 (10%) shoulder</p> <p>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</p> <p>Median age in years (range): 67 (21-88)</p> <p>Mean duration SAT: not mentioned (probably entire follow-up time)</p> <p>Excluded subjects: n=3/24</p> | <p>N/A</p> | <p>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.</p> | <p>Failure: n=7 (33%)</p> <p>Treatment success: Standard prosthesis: 90% Tumor prosthesis: 50%</p> <p>Side-effects of antibiotics: 43%</p> | <p>SIGN level of evidence:</p> <p>Risk of bias:</p> |
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Auwers et al.
1986

Study not relevant,
excluded (In Rayyan 1
maybe, 1 excluded,
selecting authors had no
access to abstract/article)

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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 level of evidence & Risk of Bias | Comments |
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| <p>Chieffo et al. 2020</p> | <p>Retrospective case series</p> <p>Setting: single-centre</p> <p>Median follow-up time in months (IQR): 32 (12-101)</p> | <p>Subjects: n=50</p> <p>Type of PJI: - n=42 hip (84%) - n=8 knee (16%)</p> <p>Type of surgery: 50 (100%) 1SR</p> <p>Median age in years (IQR): 69.3 (24.5, 97.4)</p> <p>Male sex: n=31 (62%)</p> <p>LTFU: n=1 (2%)</p> | <p>No intervention/control group</p> <p>All subjects were treated with 6 weeks of antibiotics after 1SE.</p> | <p>Remission – defined as the absence of local and systemic signs of PJI during the follow-up (minimum 1 year after the end of treatment).</p> <p>Failure – included relapse and new infections after treatment completion.</p> <p>Relapses with the same microorganism</p> <p>New infection</p> | <p>Remission n=44/49 (90%) total n=37/41 (90%) hip n=7/8 (88%) knee</p> <p>Failure n=5 (10%)</p> <p>Relapses with the same microorganism n=4 (8.2%)</p> <p>New infection: n=1 (2.0%)</p> | <p>SIGN level of evidence:</p> <p>Risk of bias:</p> | <p><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.</p> |
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| Bene et al. 2018 | Retrospective case-control study | Subjects: n=26 Cases: n=2 Controls: n=24 | No intervention/control group but comparison of group with and without reoperation-free survival. | Reoperation for infection recurrence - as defined by MSIS criteria. | Weeks of antibiotics use (mean, SD): 64.2 (66.8) - Cases: 64.2 (66.8) - Controls: 96.4 (115.3) P=0.8639 | SIGN level of evidence: | <u>Conclusion:</u> Chronic antibiotic suppression should be considered following THA I&D with head and liner exchange. |
| | Setting: single-centre | Type of PJI: - n=26 hip (100%) | Cases: subjects with a reoperation for infection recurrence during follow-up time. | Weeks of antibiotics use | 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 | Risk of bias: | |
| | Median follow-up time in years (range): 4.1 (0.4–7.7) | Type of surgery: - I&D with head and liner exchange Mean age in years (SD): 61.7 (10.7) Male sex: not stated LTFU: 0 (0%) | Controls: subjects without a reoperation for infection recurrence during follow-up time. | | | | |

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| <p>Benkabouche et al. 2019</p> | <p>RCT</p> <p>Setting: single-centre, 2SR</p> <p>Median follow-up in years: 2.2</p> | <p>Subjects n=123 I: n=62 C: n=61</p> <p>Types of infection and surgery: NB: NOT ONLY PJI n=39 (32%) 2SE for prosthetic joint infection n=44 (36%) metal plate infection n=11 (9%) intramedullary nail infection n=30 (24%) infection of other osteosynthesis</p> <p>Median age in years: 64</p> <p>Male sex: 38 (62%) I: n=17 (43.6%) C: n=14 (66.7%)</p> <p><u>Intention to treat analysis:</u> LTFU: 0 (0%)</p> <p><u>Per protocol analysis:</u> LTFU: 6 (4.9%) I: 3 (4.8%) C: 3 (4.9%)</p> | <p>I: 4-weeks antibiotics C: 6-weeks antibiotics</p> | <p>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.</p> <p>Significant antibiotic-related adverse events – Not defined</p> | <p><u>Intention to treat analysis:</u></p> <p>Remission I: n=58 (95%) C: n=58 (94%) P=0.71</p> <p>Significant antibiotic-related adverse events I: n=17 (28%) C: n=22 (35%) P= 0.36</p> <p><u>Per protocol analysis:</u></p> <p>Remission I: 57 (95%) C: 54 (95%) P=0.95</p> <p>Significant antibiotic-related adverse events I: 17 (28%) C: 19 (33%) P= 0.56</p> | <p>SIGN level of evidence:</p> <p>Risk of bias: 8/10</p> | <p><u>NB: not only PJI</u></p> <p><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.</p> <p>Study is about 2SR, not about DAIR or 1SR (amongst other non PJI infections)</p> |
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| Bernard et al. 2010 | <p>Prospective cohort study</p> <p>Setting: single-centre</p> <p>Median follow-up time in months (range): 36 (26-65)</p> | <p>Subjects n=144 I: n=70 C: n=74</p> <p>Type of PJI: - n=62 (43%) hip arthroplasties - n=62 (43%) knee arthroplasties - n=20 (14%) hip hemiarthroplasties</p> <p>Type of surgery: I: - n=20 (29%) DAIR - n=4 (6%) 1SR - n=36 (51%) 2SR - n=24 (35%) none</p> <p>C: - n=40 (54%) DAIR - n=6 (8%) 1SR - n=20 (27%) 2SR - n=27 (37%) none</p> <p>Median age in years (IQR): 77 (67-82)</p> <p>Male sex: n=69 (47.9%) I: n=32 (45.7%) C: n=37 (50.0%)</p> <p>LTFU: not stated</p> | <p>I: 6 weeks antibiotics</p> <p>C: 12 weeks antibiotics</p> | <p>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.</p> | <p>Cure: n=115 (80%) I: n=63 (90%) C: n=61 (68.9%) P= not stated</p> <p>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”.</p> | <p>SIGN level of evidence:</p> <p>Risk of bias: 5/8</p> | <p><u>Conclusion:</u> 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.</p> |
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| Chaussade et al. 2017 | Retrospective cohort study | Subjects: n=87 I: n=44 C: n=43 | I: 6 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%) | SIGN level of evidence: 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. |
| | Setting: multicentre | 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 | C: 12 weeks antibiotics | | | | |
| | Mean follow-up time in months: 52.1 | 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) | | | | | |

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| El Helou et al. 2011 | Retrospective cohort study | Subjects: n=208 I: n=82 C: n=126 | I: 4 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 level of evidence: Risk of bias: 4/8 | <u>Conclusion:</u> 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 |
| | Setting: single-centre, 2SR | 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 | C: 6 weeks iv antibiotics | | | | |
| | Mean follow-up time in years (SD): I: 6.6 (10.3) C: 4.5 (2.8) | 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 | | | | | |

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| Hsieh et al. 2009 | Retrospective cohort study | Subjects: n=99 I: n=53 C: n=46 | I: 1 week antibiotics | Free of infection - not defined in the article | Free of infection: 89 (90%) I: n=47 (89%) C: n=42 (91%) P=0.67 | SIGN level of evidence: | <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 |
| | Setting: single-centre, 2SR | Type of PJI: 99 (100%) hip | C: 4-6 weeks antibiotics | Persistent infection - defined as the presence of PHI after first-stage surgery. | Persistent infection: I: n=4 (8.5%) C: n=4 (9.5%) P= not stated | Risk of bias: 4/8 | |
| | Median follow-up time in months (range): 43 (24-60) | Type of surgery: n=99 (100%) 2SR using an interim antibiotic-loaded cement spacer in the interim | | Re-infection - PHI that occurred after the completion of SEA and antimicrobial therapy. | Re-infection I: n=3/50 (6.0%) C: n=2/44 (4.5%) P= not stated | | |
| | | Median age in years (range): I: 62 (28-76) C: 59 (22-81) | | Medical costs | Medical costs I: \$13732 C: \$21756 P=<0.001 | | |
| | | Male sex: n=60 (60.6%) I: n=33 (62.3%) C: n=27 (58.7%) | | Hospital stay | Hospital stay in days I: 18 C: 43 P=<0.001 | | |
| | | LTFU: 8 I: 3 C: 5 | | Complications related to systemic antibiotic therapy | Complications related to systemic antibiotic therapy I: 0 (0%) C: 5 (11%) P= not stated | | |

Lora-Tamayo et al. 2016

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| RCT | <u>Intention to treat analysis</u> | I: 8 weeks of levofloxacin plus rifampicin | 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> | SIGN level of evidence: | <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. |
| Setting: multicentre (17 centres) | Subjects: n=63 I: n=30 C: n=33 | C: 3 months or 6 months of levofloxacin plus rifampicin for hip and knee PJI respectively | | 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%) | Risk of bias: 5/10 | |
| <u>Intention to treat analysis:</u> Median follow-up time in days (IQR): 540 (not mentioned) | Type of PJI: I: 11 (37%) hip 19 (63%) knee C: 18 (55%) hip 15 (45%) knee | | | <u>Per protocol analysis</u> | | 100% levofloxacin and rifampicin treatment 100% staphylococcal PJI |
| | Type of surgery: n=63 (100%) DAIR | | | 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%) | | |
| | 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 | | | | | |

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| <p>Ma et al. 2019</p> | <p>Retrospective cohort study</p> <p>Setting: Single-centre, 2SR</p> <p>Mean follow-up time in months (SD): 75.3 (30.6)</p> | <p>Subjects: n=63 I: n=21 C: n=43</p> <p>Type of PJI: n=63 (100%) knee</p> <p>Type of surgery: n=63 (100%) 2SR</p> <p>Mean age in years (SD): 70.3 (11.0) I: 71.9 (8.2) C: 69.5 (12.2)</p> <p>Male sex: n=21 (32.8%) I: n=3 (14.3%) C: n=18 (41.9%)</p> <p>LTFU: not mentioned</p> | <p>I: <1 week of antibiotics</p> <p>C: 4-6 weeks of antibiotics</p> | <p>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.</p> <p>Re-resection arthroplasty</p> | <p>Re-resection arthroplasty survival after 5 years I: 95.0% C: 75.8%</p> <p>- Kaplan-Meier survival analysis showed the survival rate of I group was not inferior to C group. <i>P</i>=0.08</p> <p>Implant failure survival after 5 years I: 85.2% C: 74.0%</p> <p>- Kaplan-Meier survival analysis showed the survival rate of I group was not inferior to C group. <i>P</i>=0.317</p> | <p>SIGN level of evidence:</p> <p>Risk of bias: 3/8</p> | <p><u>Conclusion:</u> 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.</p> <p>Study is about 2SR, not about DAIR or 1SR</p> |
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| Puhto et al. 2011 | <p>Retrospective cohort study</p> <p>Setting: Single-centre</p> <p>Mean follow-up time in months (SD): I: 26.2 (12) C: 50.6 (29)</p> | <p><u>Intention to treat analysis:</u> Subjects: n=132 I: n=72 C: n=60</p> <p>LTFU: 4</p> <p><u>Per protocol analysis:</u> Subjects: n=86 I: n=48 C: n=38</p> <p>Type of PJI: n=32 (37%) hip n=54 (63%) knee</p> <p>Type of surgery: n=86 (100%) DAIR</p> <p>Mean age in years (SD): I: 70 (10.4) C: 65 (9.9)</p> <p>Male sex: n=21 (32.8%) I: n=21 (44%) C: n=18 (47%)</p> | <p>I: 3 or 2 months of antibiotics for hip and knee PJI respectively</p> <p>C: 6 or 3 months of antibiotics for hip and knee PJI respectively</p> | <p>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.</p> | <p><u>Intention to treat analysis:</u> Treatment success I: 42 (58.3%) C: 34 (56.7%) p=0.85</p> <p><u>Per protocol analysis:</u> Treatment success I: n=42 (87.5%) C: n=34 (89.5%) P=0.78</p> | <p>SIGN level of evidence: Risk of bias: 4/8</p> | <p><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.</p> |
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| <p>Spitzmuller et al. 2019</p> | <p>Case-control study</p> <p>Setting: multicentre (3 academic referral institutions)</p> <p>follow-up time: 1 year</p> | <p>Subjects: n=269 Cases: n=59 Controls: n=210</p> <p>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</p> <p>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</p> <p>Median age in years (IQR): Cases: 63 (48-71) Controls: 67 (55-73)</p> <p>Male sex: Cases: 42 (71%) Controls: 106 (50%)</p> | <p>Case: subjects who sustained any reinfection demanding any surgical revision ≤ 1 year after the index procedure.</p> <p>Controls: subjects who did not sustain any infection demanding surgical revision (or any surgical revision for infection) ≤ 1 year</p> | <p>Duration of antibiotic treatment</p> | <p>Univariate analysis: suggested an increased risk of recurrent infection with ≥ 14 days antibiotic treatment: OR (95% CI) 1.82 (1.00-3.28) $P=0.049$</p> <p>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), $P=0.055$</p> | <p>SIGN level of evidence:</p> <p>Risk of bias:</p> | <p>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.</p> <p><u>Conclusion:</u> The optimal duration of systemic antibiotic treatment with surgical concepts of curing wound and device-related orthopaedic infections is still unclear.</p> |
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| Yen et al. 2019 | Systematic review and meta-analysis | <p>Subjects: n=856 I: 465 C: 580</p> <p>Included studies: 1 RCT and 9 observational studies</p> <p>Type of joints: knees, hips, shoulders, ankles or elbows.</p> <p>Type of surgeries: DAIR, 2SR, 1SR</p> <p>Range median/mean age: 61-77 years</p> <p>Range proportion of men: 45-55%</p> | <p>I: short-course of antibiotics</p> <p>C: long-course of antibiotics</p> | <p>Clinical event - defined as an event which included PJI-related death, re-infection and persistent infection</p> | <p>Clinical event I: 99 (21%) C: 141 (24%)</p> <p>Meta-analysis showed no significant difference between short-course and long-course antibiotics: RR (95% CI) 0.87 (0.62–1.22), <i>P</i>=0.051</p> <p>The older the studied group was, the more short-course antibiotics were favoured.</p> | <p>SIGN level of evidence:</p> <p>Risk of bias: 12/14</p> | <p><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.</p> <p><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.</p> |
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1 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 =
2 intervention group; IQR = interquartile range; LTFU = lost to follow-up; n = number; *P* = p-value; PJI = prosthetic joint infection
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