Prosthetic joint infections: new diagnostic and therapeutic strategies

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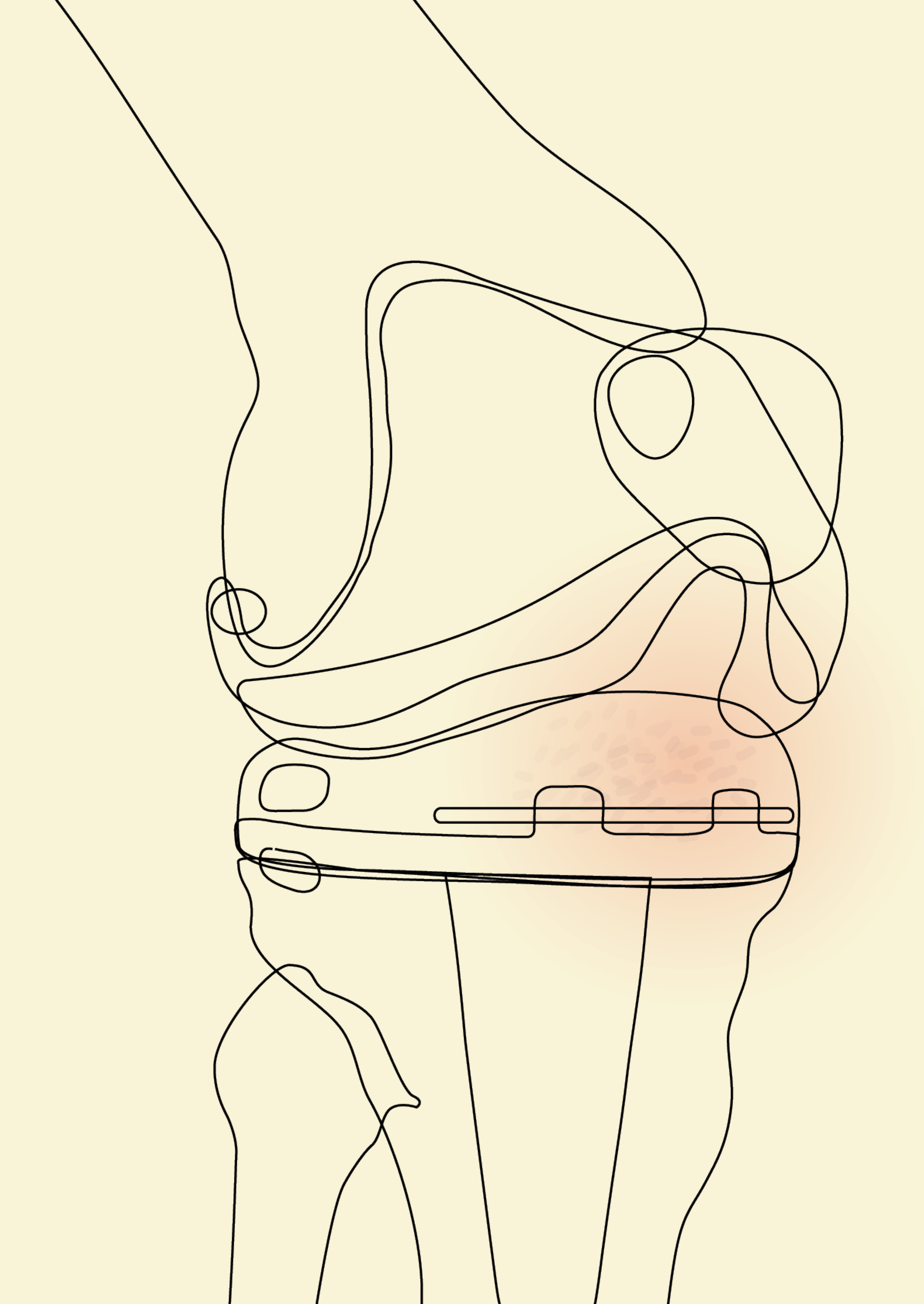

Part II. Evaluation of current antimicrobial strategies for PJI

CHAPTER 4

Outcome of debridement, antibiotics and implant retention for staphylococcal hip and knee prosthetic joint infections, focused on rifampicin use: a systematic review and meta-analysis.

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Abstract

The treatment of staphylococcal prosthetic joint infection (PJI) with debridement, antibiotics and retention of the implant (DAIR) often results in failure. An important evidence gap concerns the treatment with rifampicin for PJI. A systematic review and meta-analysis were conducted to assess the outcome of staphylococcal hip and/or knee PJI after DAIR, focused on the role of rifampicin. Studies published until September 2nd, 2020 were included. Success rates were stratified for type of joint and type of micro-organism. Sixty-four studies were included. The pooled risk ratio for rifampicin effectiveness was 1.10 (95% CI 1.00-1.22). Pooled success rate was 69% for S. aureus hip PJI, 54% for S. aureus knee PJI, 83% for CNS hip PJI and 73% for CNS knee PJI. Success rates for MRSA PJI (58%) were similar to MSSA PJI (60%). The meta-analysis indicates that rifampicin may only prevent a small fraction of all treatment failures.

Introduction

A prosthetic joint infection (PJI) is a severe complication of orthopedic surgery and associated with significant morbidity and mortality. *Staphylococcus aureus* (*S. aureus*) or Coagulase-negative staphylococci (CNS) are the most common causative pathogens of PJI, accounting for about two-third of all cases[1]. Treatment of acute PJI, aimed at maintaining the implant, consists of thorough surgical debridement of the implant and of the infected tissue around the implant, followed by antibiotic treatment (summarised as DAIR: Debridement, Antibiotics and Implant Retention). Nevertheless, failure rates with this treatment strategy are high, ranging from 10% to 45% in some of the largest studies[2, 3]. An important evidence gap concerns the causes for these high failure rates. The type of joint, the type of micro-organism and the antibiotic treatment that was used for PJI are risk factors that have been put forward to explain these high failure rates. Most international guidelines have adopted rifampicin combination therapy as the cornerstone antibiotic treatment for staphylococcal PJI treated with DAIR, based on experimental animal models, one randomised trial and several cohort studies. However, rifampicin combination therapy is associated with significant side effects and drug-drug interactions, making its use less patient-friendly [4, 5]. Moreover, the literature regarding the effect of rifampicin combination therapy against staphylococcal hip and knee PJI after DAIR has not yet been explored systematically. Most observational PJI studies also included patients with PJI caused by other micro-organisms. Furthermore, not all studies specify details regarding the outcome per affected joint (hip or knee) or per causative staphylococcal species (*S. aureus* or CNS), both of which may influence success rate. Therefore, we conducted a literature search to systematize and appraise the available evidence concerning outcome of staphylococcal PJI treated with DAIR, with a specific focus on the outcome with or without rifampicin use. A secondary objective was to relate outcomes to the type of joint (hip or knee), the type of micro-organism (*S. aureus* and CNS) and susceptibility to methicillin (methicillin-resistant *S. aureus*, MRSA and methicillin-sensitive *S. aureus*, MSSA).

Methods

Search strategy and selection criteria

The reporting of this systematic review and meta-analysis is in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement. The population of interest included all patients evaluating the outcome after DAIR for the treatment of staphylococcal hip and/or knee PJI, as defined by IDSA or MSIS criteria[6]. Studies that also included other types of surgical strategy, other joints or other micro-organisms were only included if the outcome was quantified separately for the variables of our interest. The following exclusion criteria were applied: Studies that included patients with superficial wound infection, case reports and studies reporting 20 patients or less with staphylococcal PJI[7]. A meta-analysis was performed for the studies in which patients treated with rifampicin could be compared with patients not treated with rifampicin. The search was limited to articles published until September 2nd, 2020. Articles were identified searching PubMed, Cochrane Library and Embase databases (Supplemental Table 1). In addition, bibliographies of relevant articles were cross-checked for references missing in the original search. Two independent reviewers (H.S. and L.M.G.) reviewed all studies. A third reviewer (MdB) was consulted if disagreements between reviewers could not be solved.

Table 1. Reported outcome after DAIR, stratified for micro-organism and/or type of joint using individual patient data from 64 included studies

Micro-organism and/or type of joint	n studies*	n patients*	pooled success rate of all individual patient data	RR (95%CI)#
All	64	4380	60%	-
Per micro-organism				
S. aureus	54	2922	61%	ref.
CNS	36	761	74%	1.50 (1.32-1.70)
Per affected joint				
Knee	27	1106	55%	ref.
Hip	24	904	69%	1.45 (1.29-1.63)
Per affected joint *and* micro-organism				
S. aureus knee PJI	19	692	54%	ref.
CNS knee PJI	12	187	73%	1.72 (1.33-2.21)
S. aureus hip PJI	19	547	69%	1.48 (1.27-1.72)
CNS hip PJI	13	145	83%	2.66 (1.85-3.84)

* The columns 'n studies' and 'n patients' displays the number of studies and patients for which the specific outcome regarding affected joint and/or micro-organism was reported. For example: one study could report outcome for both *S. aureus* and CNS but not stratifying outcome for type of joint, while other studies only reported outcome for the total population without stratification for either type of joint or micro-organism. Therefore, numbers in this table cannot be summed.
# Relative Risks for success were calculated for micro-organisms (with *S. aureus* PJI as reference), for type of joint (with knee PJI as a reference) and for the 4 groups (with *S. aureus* knee PJI as a reference).

Data analysis

Texts of selected abstracts were reviewed, as were article texts of abstracts that could not be excluded based on abstract review alone. Data from each study were entered in an SPSS database. Information extracted included study design, number of patients with *S. aureus* and/or CNS PJI, number of hip and/or knee PJI, year of publication, duration of follow-up, rifampicin use (number of patients receiving rifampicin) and treatment outcomes for all these subcategories. As there is no universally accepted definition for treatment success or failure after PJI, the definitions used by the included paper were used. We contacted study authors and requested individual patient-level data if rifampicin data were not clearly specified.

Assessment of quality of evidence

Estimates of associations in observational studies may deviate from true underlying relationships due to confounding or biases. Confounding may occur as patients with comorbidity or use of immunosuppressants, implying a higher a priori risk for a poor outcome, may not be selected for rifampicin treatment. Survival bias occurs when only patients 'surviving' the first weeks after debridement are included in the rifampicin group. The Newcastle-Ottawa Quality Scale was used to assess the quality of the studies included in the meta-analysis (Supplemental table 3). As this scale only addresses basic methodological factors and not important confounding factors or survival bias, studies will also be reviewed qualitatively in the discussion.

Statistical methods

For the meta-analysis, we used the Hedges random-effects model to pool the risk ratio (RR) of individual studies in order to estimate an overall RR along with its associated confidence interval (CI). The choice for a random effects method was based on the assumption that underlying risk factors for outcome were expected to vary between studies regarding underlying host comorbidities, type of joint and the severity of PJI. Patients were excluded from the meta-analysis if failure occurred in the first week after debridement and before initiation of rifampicin, to prevent survivor bias. The extent of statistical heterogeneity was assessed by calculating I^2 statistics. A funnel plot was constructed for studies reporting the primary outcome to assess the possibility of publication bias. Success rates were compared in predetermined subgroups (hip versus knee, *S. aureus* versus CNS, MRSA versus MSSA) using *t test*. A linear regression model, including success rate, proportion of rifampicin use and type of joint was used to further explore the relationship between rifampicin use and success rates. Descriptive statistics were performed using SPSS 23.0 (IBM Corp., Amonk, NY: USA). Stata was used for the meta-analysis (StataCorp, version 16, Texas, USA). The study-protocol was registered a-priori with PROSPERO (registration number CRD42020155132).

Results

Study selection and study characteristics

The review process identified 2186 articles, of which 263 full text articles were assessed for eligibility (Figure 1). In total, 64 studies (4380 patients) were included, published between 1990 and September 2nd, 2020 (Supplemental Table 2). Only two studies were published before 2005. All studies were observational cohort studies (3 prospective, 59 retrospective), except for two randomized controlled trials. The median study size was 50 patients; ten studies included more than 100 patients. *S. aureus* was the causative micro-organism in 3142 patients, CNS in 915 patients and the staphylococcal species was not specified in 323 patients. Of 1797 patients with *S. aureus* PJI in which the methicillin susceptibility of the isolates was reported, 416 (21%) were MRSA. Use of rifampicin for staphylococcal PJI was mentioned in 49 studies. Of those studies, outcome of treatment with or without rifampicin was reported in 30 studies (Table 2, also Supplemental Table 4). Except for one RCT, no studies compared baseline characteristics between patients treated and not treated with rifampicin. The study by Karlsen and colleagues was the only randomised controlled trial that could be included in the meta-analysis. In this study, 48 patients with staphylococcal PJI were randomised between rifampicin combination therapy (23 patients) and beta-lactam monotherapy (25 patients).

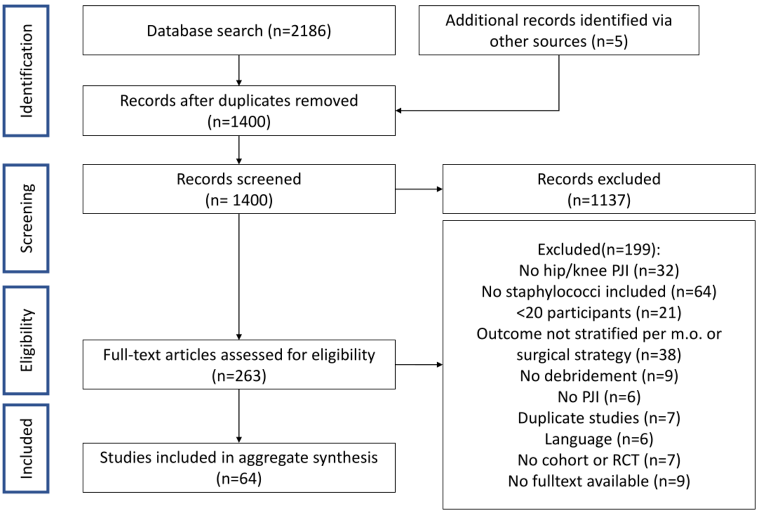

Figure 1. Flow chart of study selection.

Outcome after DAIR related to micro-organism

Outcome of treatment for staphylococcal PJI is presented in table 1. The pooled success rate in all included studies was 60%. In smaller cohorts (<100 patients), the reported success rates varied from 23% to 90% (figure 4). Cure rates in the two largest cohort studies (both containing more than 300 patients and likely more closely reflecting a real-life clinical situation) were 54% and 56%[2, 8]. Pooled success rate for *S. aureus* PJI after DAIR was 62% (2922 analyzed patients in 54 studies) and for CNS PJI 73% (36 studies, 760 patients; table 1). Outcome for MRSA and MSSA PJI was reported in 25 and 28 studies, respectively (table 3); success rate after DAIR was not different between both groups (MRSA 58%, MSSA 60%, p=0.459). Outcomes between MRSA and MSSA PJI were not different when stratified for type of joint (data not shown). Pooled success rate of *S. aureus* PJI after DAIR was 67% if PJI occurred within 3 months after arthroplasty and 49% in patients with later onset of *S. aureus* PJI (990 analysed patients in 9 studies)[2, 9-16] .

Outcome after DAIR related to type of joint

Outcome per affected joint was specified in 33 studies. Pooled success rate after DAIR for *S. aureus* hip PJI was 69%, while pooled success rate after *S. aureus* knee PJI was 54% (table 1). Pooled success rates after DAIR for CNS hip PJI was 83% and 73% for CNS knee PJI. Using linear regression analysis, reported success rates positively correlated with the proportion of included hip PJI per study: success rates increased from 54% in studies with <25% of patients with hip PJI to 82% in studies with >75% of patients with hip PJI (p=0.002), indicating that reported outcome of PJI is strongly affected by the type of joint included in studies (figure 5). The high success rates for hip PJI could not be attributed to rifampicin use: success rates were 83% for patients on rifampicin and 82% for patients who were not treated with rifampicin (RR 1.01, 95% CI 0.85-1.20; evaluable in four studies with 157 patients, table 2).

Table 2. Outcome of 30 studies that reported individual patient data regarding the use of rifampicin or not.

	N studies	N patients	Cure with rifampicin[#]	Cure without rifampicin[#]	RR (95%CI)
Hip PJI[*]					
S. aureus	0				
CNS	0				
Combined	4	157	102/123 (83%)	28/34 (82%)	1.01 (0.85-1.20)
Knee PJI[*]					
S. aureus	1	22		9/22 (41%)	
CNS	0				
Combined	2	108	56/69 (81%)	17/34 (50%)	1.62 (1.14-2.31)
Hip and knee PJI[$]					
S. aureus	3	135	100/125(80%)	4/10 (40%)	2.00 (0.93-4.29)
CNS	0				
Combined	24	1652	903/1298 (70%)	186/354 (53%)	1.32 (1.19-1.47)

[#]Pooled individual patient data in N studies
[*]Per category studies are included if outcome is reported apart for *S. aureus* and/or CNS apart or combined if outcome for all staphylococci is summarized
[$]Studies are included in this category if outcome was reported only for hip and knee PJI together

Table 3. Outcome of MSSA versus MRSA PJI treated with DAIR

Study	N studies*	N patients	Pooled success rate#
MSSA PJI	28	1381	60%
MRSA PJI	26	416	58%
Hip MSSA PJI	2	32	81%
Hip MRSA PJI	1	12	92%
Knee MSSA PJI	3	56	66%
Knee MRSA PJI	3	78	64%

*Per category, studies were included if they reported specific or combined outcome for hip and/or knee MSSA and MRSA.
based on individual patient data
MSSA: methicillin-susceptible *Staphylococcus aureus*, MRSA: methicillin-resistant *Staphylococcus aureus*

Outcome after DAIR related to treatment with rifampicin

The reported success rates over the years, stratified by treatment with rifampicin, are shown in figure 2. Success rates were higher in studies in which rifampicin was prescribed (64% in 34 studies with 2884 patients) compared to studies in which rifampicin was not prescribed or not mentioned by the authors (44% in 18 studies with 976 patients). In twelve studies, all included patients were treated with rifampicin resulting in a pooled success rate of 71% (table 2). These studies were likely hampered by selection bias because outcome of patients who did not use rifampicin were not evaluated herein. Twelve observational studies and one randomized controlled trial reported outcome for both patients treated and not treated with rifampicin. In two of these studies, the group of patients without rifampicin was too small for comparative evaluation[17, 18]. Outcome of the remaining 11 studies was evaluated with a random effects meta-analysis (figure 3). Survivor bias could be corrected in two of those studies, in which 5 out of 17 and 6 out of 13 patients failed before initiation of rifampicin[19, 20]. From one study, comparing two historical groups and one prospective group, only the historical groups were included in the meta-analysis because these groups could be compared with each other while a control group for the prospective cohort was absent. The only included RCT in the meta-analysis (by Karlsen and colleagues) reported similar cure rates between the rifampicin group (74%) and the beta-lactam group (72%)[21]. The pooled risk ratio for rifampicin effectivity from 11 studies in the meta-analysis was 1.10 (95% CI 1.00-1.22). The funnel plot was asymmetric (Supplemental Figure 1). A trim-and-fill analysis to explore this possible publication bias suggested four missing studies, which after correction would result in an adjusted relative risk for success of 1.04 (95%CI 0.94 tot 1.14).

Figure 2. Success rates over the years for staphylococcal PJI treated with DAIR and related to use of rifampicin. Different bubble sizes represent differences in study size

Discussion

Despite gradually improving success rates over the years, the reported outcome of staphylococcal PJI is still heterogeneous, ranging from 23% to 90%. Overall, the pooled risk ratio for success was slightly higher in patients treated with rifampicin. Success rates were considerably better for hip and CNS PJI than for knee and *S. aureus* PJI. Success rates of MRSA and MSSA PJI after DAIR were similar. Of note, the ratio of *S. aureus* to CNS PJI remained stable over the years (between 72-76%), indicating that success rates are probably not influenced by changing epidemiology of causative staphylococci.

The pooled estimated effect of rifampicin on treatment outcome in our meta-analysis differs from a recently published meta-analysis that did not find a positive association between treatment with rifampicin and success rates[22]. Several studies in that meta-analysis included other micro-organisms than staphylococci or patients with other surgical strategies whom we excluded[23-26]. Moreover, with a broader search strategy, we were able to include seven other studies in our meta-analysis.

Interpreting the association between rifampicin and success rates after DAIR in the meta-analysis is complicated by survival bias and selection bias, as ten studies in the meta-analysis were observational. In three studies, survival bias could be ruled out by excluding patients who failed early after debridement and before start of rifampicin, [2, 19, 20] but survival bias was likely present in more studies. The positive association between duration of rifampicin and success rates after DAIR in the study of Becker and colleagues could be explained by survival bias and selectively excluding patients from the analysis who developed a failure while on rifampicin treatment[27, 28]. Lora-Tamayo and colleagues described the strongest association between rifampicin use and outcome. This study addressed survivor bias and performed multivariate regression analysis to correct for confounding factors, which did not change the outcome of the study[2]. The trim- and fill- analysis suggested that publication bias have influenced the outcome of the meta-analysis. However, this analysis is a statistical measure that presumes that negative studies were not published, which in our opinion is not very likely given the many studies presented in this review with negative results.

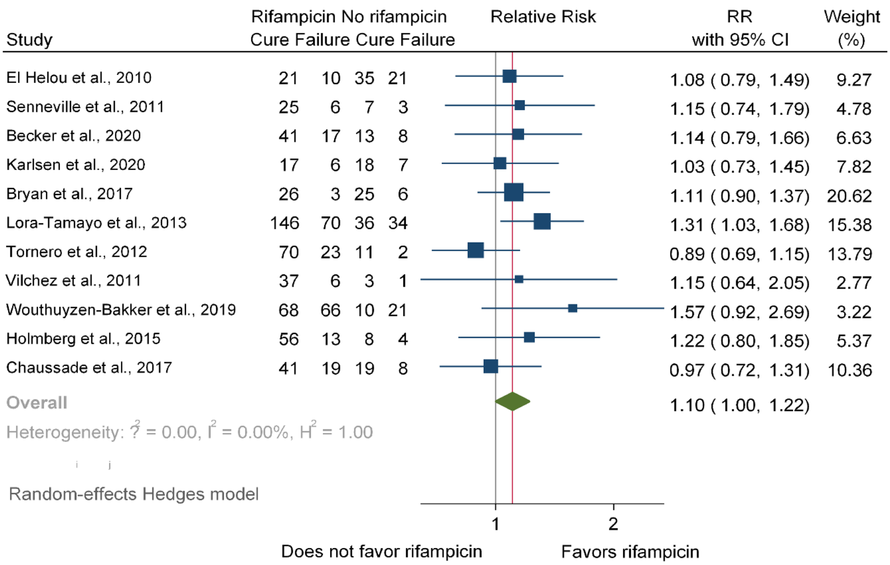

Figure 3. Meta-analysis of 11 studies in which outcome for staphylococcal PJI after DAIR could be compared between patients treated and not treated with rifampicin

The point estimate (relative risk, RR) for each study is represented by a square. The 95% CI for each study is represented by a horizontal line intersecting the square. The size of the square represents the relative precision of the study estimates: the bigger the square the more precise the study was.

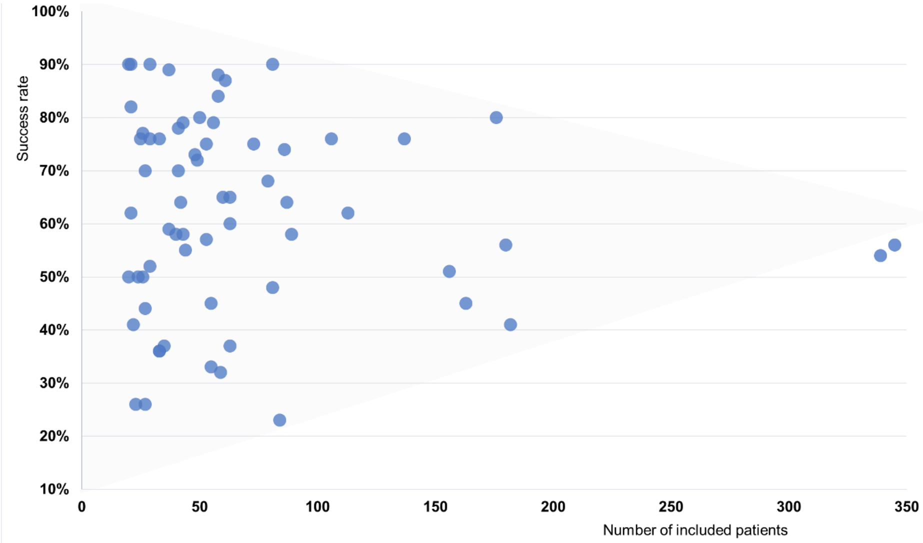

Figure 4. Relation between study size and outcome of staphylococcal PJI treated with DAIR (n = 64 studies)

As most studies in this review were observational, confounding factors that influence both the choice for antibiotic strategy and outcome after DAIR were present in these studies. Unfortunately, a comparison of baseline characteristics between rifampicin and non-rifampicin users is nearly absent in the literature summarised in this review. Survival bias may explain the increased effectiveness of long-term rifampicin compared to short-term rifampicin in the study of Lesens and colleagues, because these patients were only analysed in the group with long-term rifampicin if experience treatment failure during the first weeks of treatment[11]. Confounding by indication was described in the studies of Morata and colleagues and Ascione and colleagues in which patients who were not treated with rifampicin had diabetes, rheumatoid arthritis and liver disease more often[23, 26].

The well-known RCT of Zimmerli and colleagues (1998) was excluded from this review due to the low number of patients (18 patients with PJI of whom eight received rifampicin) and because outcome was not stratified per micro-organism (both *S. aureus* and CNS included) and type of infection (both osteosynthesis-associated infection and PJI were included). Patients were randomised in this trial between rifampicin combination therapy or ciprofloxacin monotherapy[29]. 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 in the outcome as four out of five failures this group were due to ciprofloxacin resistance. The RCT of Karlsen and colleagues contained three times as much patients than the trial of Zimmerli and colleagues and had a different comparator arm (beta-lactams instead of ciprofloxacin)[21] .

The timing of rifampicin initiation and the duration of treatment with rifampicin may also affect outcome. In the two randomized controlled trials discussed above and one observational study, rifampicin was started immediately or from day one postoperatively[21, 29, 30]. In these studies, rifampicin resistance had not developed in patients with positive cultures after failure. Rifampicin resistance in patients with failure after DAIR has been reported, but this was in patients who were not treated with adequate debridement or with combination therapy[31, 32]. Whether the duration of rifampicin combination therapy affects outcome is not sure. Treatment duration was three months in most studies included in this review. In some observational studies, shorter rifampicin treatment was associated with more treatment failure, but these results should be interpreted cautiously as studying treatment duration in observational studies is inherently affected by selection bias and survival bias[11, 27, 28]. More research is needed to gain more evidence regarding the timing and duration of rifampicin.

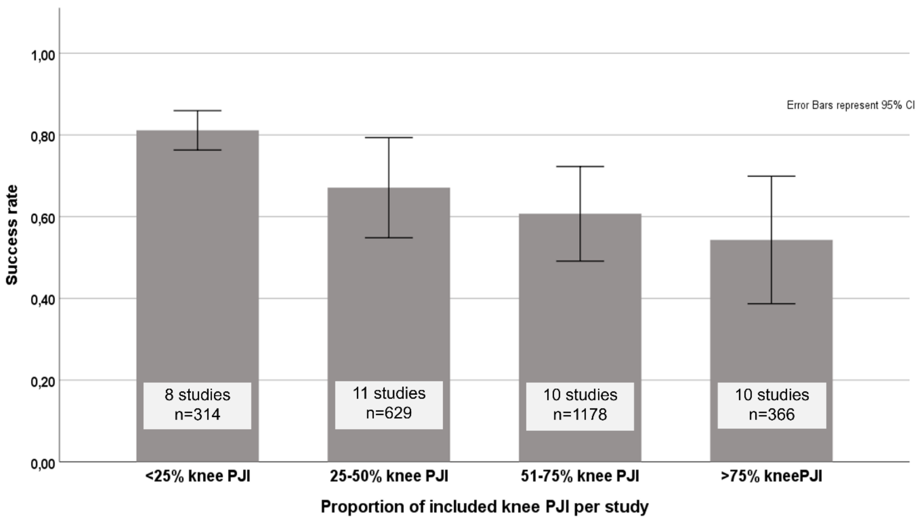

Figure 5. Success rates in 39 studies that could be categorized by knee-to-hip-ratio

This review reveals that success rates are strongly influenced by the ratio of knee-to-hip PJI per study. Are higher success rates, usually attributed to rifampicin use, in fact explained by a decreased knee-to-hip ratio in studies? To explore this further, we related the knee-to-hip ratio to rifampicin use. We unexpectedly found that the knee-to-hip ratio per study was inversely related to rifampicin use. The knee-to-hip PJI ratio in studies was 0.90 (meaning more knees than hips) if rifampicin was not used, 0.77 if rifampicin use was not mentioned, 0.40 if a certain proportion of patients used rifampicin and 0.35 in studies in which all patients were treated with rifampicin. As a derived measure we performed linear regression analysis with proportion of rifampicin use per study as predictor variable for success weighted by proportion of included knee PJIs. Results revealed that the significant correlation between rifampicin use and successful outcome ($p=0.01$) disappeared after correction for type of joint ($p=0.17$), indicating that both rifampicin and type of joint influence the outcome of PJI. We hypothesize that adjunctive rifampicin use will not yield a further increase in success rate in patients with hip PJI with a priori higher chances for cure. The poor outcomes of knee PJI may relate to the surgical debridement, which is more complicated for infected knee prostheses than for hip prostheses due the anatomical barriers that hinder a proper debridement of a knee prosthesis. Of note, outcome for knee PJI was better in patients treated with rifampicin (81%) compared to patients not treated without rifampicin (50%) (RR 1.62 (1.14-2.31), but this risk ratio could be obtained from only two studies.

The definition of treatment failure varied across included studies. In most studies a second debridement within the first three weeks of antibiotic treatment was not regarded as failure, while other studies defined all subsequent debridements as failure. Further, the use of chronic suppressive antibiotic therapy with a well-functioning prothesis is defined as a failure in some but not all studies, also affecting cure rates in studies[33]. Of all included studies, 30 studies did not report whether chronic antibiotic suppression was part of the definition of failure or was regarded as success in patients with a functioning prosthesis. Of note, success rates ware comparable between 30 studies that defined chronic suppressive antibiotics as failure (61%) and 34 studies that did not mention suppressive therapy or regarded suppressive therapy as success (60%), but interpretation is difficult as most studies did not specify the number of patients on suppressive antibiotic treatment. Uniform definitions of treatment failure are needed making comparison between studies more accurate.

In this review, higher success rates were reached in early postoperative PJI (within 3 months after arthroplasty) compared to later onset of PJI. Wouthuyzen-Bakker and colleagues reported lower treatment success of late acute (hematogenous) PJI compared to early postoperative PJI for both *S. aureus* (34% versus 75%) and CNS (46% versus 88%).

Poor outcome of late acute PJI may relate to the hematogenous origin with seeding of inaccessible parts of the prosthesis like the stem which cannot be surgically debrided possibly resulting in more treatment failure.

Taken together, this review and meta-analysis found that the outcome of staphylococcal PJI after DAIR is largely determined by the type of joint and the type of causative micro-organism. Outcome for MRSA PJI seems to equal outcome for MSSA PJI. Use of rifampicin was associated with a 10% increase in success rate, but studies were hampered by confounding, publication bias and selection bias. The supporting evidence for rifampicin combination treatment is weak and possibly restricted to knee PJI, but good-quality data from randomized studies are scarce. Given this paucity of evidence, the accumulated data expose an urgent need to address the role and duration of rifampicin for staphylococcal PJI in a large randomized controlled trial.

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Author contributions
All authors participated in the study design, data interpretation and the writing of the manuscript and agreed to be accountable for all aspects of the work.

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Potential conflicts of interest
All authors: no reported conflicts of interest.

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Supplementary Data

Supplemental table 1. Search strategy

Databases:	**Pubmed, Embase, Cochrane Library**
Search terms:	((“Debridement”[Mesh] OR “debridement”[tw] OR debrid*[tw] OR “DAIR”[tw] OR “debridement, antibiotics and implant retention”[tw] OR “debridement, antibiotics and implant retention dair”[tw] OR “debridement, antibiotics, and implant retention”[tw] OR “implant retention”[tw]) AND (“Prosthesis-Related Infections”[mesh] OR “Prosthesis Infection”[tw] OR “Prosthesis Infections”[tw] OR “Prosthetic Infection”[tw] OR “Prosthetic Infections”[tw] OR “Prosthetic Joint Infection”[tw] OR “Prosthetic Joint Infections”[tw] OR “Prosthesis-Related Infections”[tw] OR “Prosthesis-Related Infection”[tw] OR “peri prosthetic joint infection”[tw] OR “peri prosthetic joint infections”[tw] OR “periprosthetic joint infection”[tw] OR “periprosthetic joint infections”[tw] OR ((“Joint Prosthesis”[Mesh] OR “Arthroplasty, Replacement”[Mesh]) AND (“Infection”[mesh] OR infect*[tw] OR “deep infection”[tw] OR “Wound Infection”[mesh] OR “Sepsis”[mesh] OR “Surgical Wound Infection”[mesh])) OR ((“Prosthesis”[tw] OR prosthe*[tw]) AND (“Joint”[tw] OR “Joints”[tw] OR “Joints”[Mesh] OR “knee”[tw] OR “shoulder”[tw] OR “elbow”[tw] OR “hip”[tw] OR “knees”[tw] OR “shoulders”[tw] OR “elbows”[tw] OR “hips”[tw]) AND (“Infection”[mesh] OR infect*[tw] OR “deep infection”[tw] OR “Wound Infection”[mesh] OR “Sepsis”[mesh] OR “Surgical Wound Infection”[mesh]))) AND (“succes rate”[tw] OR ”success rates”[tw] OR ”success”[tw] OR succes*[tw] OR “failure rate”[tw] OR ”failure rates”[tw] OR ”failure”[tw] OR fail*[tw] OR ”infection control”[tw] OR ”Treatment Outcome”[mesh] OR ”Treatment Outcome”[tw] OR ”outcome”[tw] OR ”outcomes”[tw]))

Supplemental table 2. Selected studies for systematic review

Included studies (n=64)	**Year**	**Type of study**	**n**	**%cure total**	**CNS**	**Saureus**	**Knee**	**Hip**	**Cure kneePJI**	**Cure hipPJI**	**Followup**
Lora-Tamayo[1]	2013	R	345	56%	NA	345	195	146	65%	66%	NA
Lora-Tamayo[2]	2013	R	44	55%	NA	44	NA	NA	NA	NA	<1yr
Shohat[3]	2019	R	113	62%	NA	113	NA	NA	NA	NA	>1yr
Duque[4]	2017	R	29	52%	NA	NA	29	0	52%	NA	>1y
Bedair[5]	2020	R	156	51%	NA	NA	92	64	44%	61%	>2y
Azzam[6]	2010	R	59	32%	NA	NA	NA	NA	NA	NA	>1y
Cobo[7]	2011	P	43	58%	NA	-/43	NA	NA	NA	NA	>1y
Fehring[8]	2013	R	63	37%	NA	NA	NA	NA	NA	NA	>2y
Theis[9]	2007	R	33	36%	NA	NA	11	22	NA	NA	NA
Senneville[10]	2011	R	41	78%	NA	NA	NA	NA	NA	NA	>3y
Tornero[11]	2015	R	176	80%	95	81	NA	NA	72%	85%	NA
Buller[12]	2012	R	182	41%	75	113	NA	NA	NA	NA	>1y
Tornero[13]	2012	R	106	76%	49	57	67	39	NA	NA	>2y
Tschudin-Sutter[14]	2016	P	81	90%	43	38	25	57	NA	NA	>2yr
Barberan[15]	2006	R	60	65%	39	21	28	32	57%	72%	>1y
Holmberg[16]	2015	R	86	74%	33	53	86	0	74%	NA	>2y
Morata[17]	2014	R	42	64%	33	9	NA	NA	NA	NA	>1yr
Wouthuyzen-Bakker[18]	2019	R	163	45%	30	141	120	44	NA	NA	NA
El Helou[19]	2010	R	87	64%	30	57	NA	NA	NA	NA	<1y
Koyonos[20]	2011	R	84	23%	28	56	NA	NA	NA	NA	>1y
Jacobs[21]	2019	R	56	79%	27	29	NA	NA	NA	NA	>1y
Wouthuyzen-Bakker[22]	2020	R	180	56%	26	154	91	62	NA	NA	>1y

Supplemental table 2. Continued

Included studies (n=64)	Year	Type of study	n	%cure total	CNS	Saureus	Knee	Hip	Cure kneePJI	Cure hipPJI	Followup
Byren[23]	2009	R	73	75%	26	47	NA	NA	NA	NA	NA
Chaussade[24]	2017	R	37	59%	25	12	NA	NA	n	NA	>1y
Fink[25]	2017	R	49	72%	25	24	NA	NA	NA	NA	>2y
Marculescu[26]	2006	R	55	33%	23	32	NA	NA	NA	NA	>1yr
Grammatopoulos[27]	2017	R	61	87%	22	39	0	61	NA	87%	>1y
Bryan[28]	2017	R	58	84%	21	37	0	58	NA	84%	>2y
Peel[29]	2013	R	43	79%	19	24	15	28	93%	71%	>1yr
Parvizi[30]	2009	R	35	37%	18	17	11	24	45%	33%	>1yr
Koh[31]	2015	R	27	70%	16	11	27	0	70%	NA	>2y
Becker[32]	2020	R	79	68%	16	65	21	59	71%	68%	>2y
Zmistowski[33]	2016	R	81	48%	16	65	NA	NA	NA	NA	>1yr
Weenders[34]	2016	R	21	82%	15	7	0	21	NA	82%	>2y
Lora-Tamayo[35]	2016	RCT	63	65%	15	48	34	29	46%	58%	>1yr
Triantafyllopoulos[36]	2015	R	55	45%	14	41	55	0	45%	NA	>1yr
Soriano[37]	2006	R	25	76%	14	11	11	14	45%	100%	>1yr
Kuiper[38]	2013	R	63	60%	13	50	NA	NA	NA	NA	>1y
Dx Duffy[39]	2018	R	33	76%	12	21	33	0	76%	NA	>2y
Lizaur-Utrilla[40]	2015	R	27	26%	11	16	27	0	26%	NA	>1yr
Sendi[41]	2017	P	21	90%	11	10	0	21	NA	90%	>2y
Moojen[42]	2014	R	50	80%	11	39	0	50	NA	80%	>1yr
Swenson[43]	2018	R	40	58%	11	29	NA	NA	NA	NA	>6m
Gardner[44]	2011	R	27	44%	10	17	27	0	44%	NA	NA
Karlsen[45]	2020	RCT	48	73%	10	38	9	39	73%	67%	>2y
Ottesen[46]	2019	R	37	89%	8	29	37	0	88%	NA	>1yr
Zhang[47]	2017	R	23	26%	5	18	23	0	26%	NA	>1yr
Flierl[48]	2017	R	20	50%	4	16	NA	NA	NA	NA	>1y
Waagsbo[49]	2009	R	26	77%	3	23	0	26	NA	NA	>2y
Scheper[50]	2018	R	41	63%	11	30	19	22	44%	83%	>6m
Kuo[51]	2019	R	26	50%	2	24	NA	NA	NA	NA	>1y
Aboltins[52]	2007	R	20	90%	1	19	7	13	86%	92%	>1y
Wilson[53]	1990	R	22	41%	0	22	22	0	41%	NA	>1yr
Bene (2x:H+K)[54, 55]	2018	R	21	62%	0	21	15	6	53%	83%	>2y
Brandt[56]	1997	R	33	36%	0	33	26	7	38%	29%	>1y
Vilchez[57]	2011	R	53	75%	0	53	35	18	69%	89%	>1yr
Wouthuyzen-Bakker[58]	2018	R	58	88%	0	58	34	24	NA	NA	>3y
Betz[59]	2015	R	29	76%	0	29	0	29	NA	76%	>3y
Bouaziz[60]	2018	R	89	58%	0	89	35	54	51%	63%	>1y
Lesens[61]	2018	R	137	76%	0	137	57	77	NA	NA	>1y
Letouvet[62]	2016	R	24	50%	0	24	NA	NA	NA	NA	>1y
Löwik[63]	2019	R	339	54%	0	339	NA	NA	NA	NA	>1yr
Hirsiger[64]	2019	R	29	90%	0	29	NA	NA	NA	NA	>3y
Joulie[65]	2011	R	53	57%	0	53	NA	NA	NA	NA	>2y

The largest included study presented outcome for both *S. aureus* and coagulase-negative staphylococci (CNS) but due to many polymicrobial infections, we decided to leave out CNS from this study in the analysis to prevent a large group of duplicate outcomes[63].

4

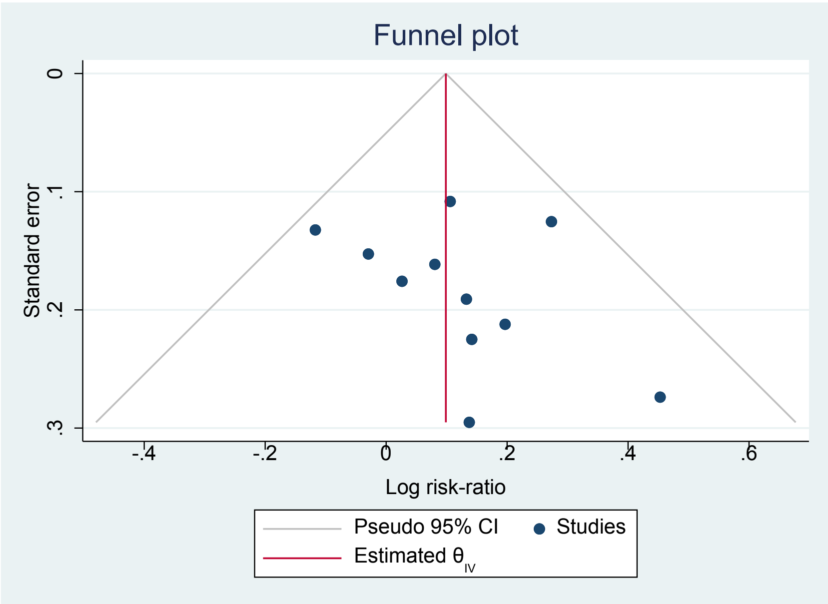
Supplemental table 3. Newcastle-Ottawa Quality assessment scale of included studies in meta-analysis

First author	Year of publication	Selection	Comparability	Outcome	Quality
Holmberg[16]	2015	****	-	***	Poor
Chaussade[24]	2017	****	**	***	Good
El Helou[19]	2010	***	-	***	Poor
Lora-Tamayo[2]	2013	****	**	**	Good
Senneville[10]	2011	****	-	**	Poor
Tornero[13]	2012	****	-	***	Poor
Vilchez[57]	2011	****	**	***	Good
Wouthuyzen-Bakker[18]	2019	****	**	***	Good
Becker[32]	2020	****	**	***	Good
Karlsen[45]	2020	****	**	***	Good
Bryan[28]	2017	****	*	***	Good

Scoring for comparability: one star was given if a regression analysis was performed including rifampicin AND type of joint or type as dependent variables, two stars were given if also other variables were included (proportion of S aureus PJI, age, comorbidity index)

Quality was registered according to Newcastle-Otawa Quality criteria:

- **Good quality**: 3 or 4 stars in selection domain AND 1 or 2 stars in comparability domain AND 2 or 3 stars in outcome/exposure domain.
- **Fair quality**: 2 stars in selection domain AND 1 or 2 stars in comparability domain AND 2 or 3 stars in outcome/exposure domain.
- **Poor quality**: 0 or 1 star in selection domain OR 0 stars in comparability domain OR 0 or 1 stars in outcome/exposure domain.



Supplemental figure 1. Funnel plot of 11 included studies in meta-analysis

Supplemental table 4. Outcome of staphylococcal PJI after DAIR in 30 studies that reported individual patient data regarding the use of rifampicin or not.

Type of joint	Rifampicin N cured/N total (%)	No rifampicin N cured/N total (%)	RR for success with rifampicin (95% CI)
Hip PJI			
Bryan	26/29 (90%)	25/31(81%)	1.11(0.90-1.37)
Moojen	37/47 (79%)	3/3 (100%)	
Waagsbo	20/26 (77%)		
Sendi	19/21 (90%)		
Total hip PJI	**102/123 (83%)**	**28/34 (82%)**	**1.01 (0.85-2.00)**
Knee PJI			
Holmberg	56/69 (81%)	8/12 (67%)	1.22 (0.80-1.85)
Wilson		9/22 (41%)	
Total knee PJI	**56/69 (81%)**	**17/34 (50%)**	**1.62 (1.14-2.31)**
Hip and Knee PJI			
Peel	31/40 (78%)	3/3 (100%)	
Wouthuyzen-Bakker 2019	68/134 (50%)	10/31 (32%)	1.57 (0.92-2.69)
Tornero	70/93 (75%)	11/13 (85%)	0.88 (0.69-1.15)
Vilchez	37/43 (86%)	4/10 (40%)	1.15 (0.64-2.05)
Senneville	25/31(81%)	7/10(70%)	1.15 (0.74-1.79)
El Helou	21/31(68%)	35/56(63%)	1.08 (0.79-1.49)
Lora-Tamayo 2013	146/216 (68%)	36/70 (51%)	1.31 (1.03-1.68)
Karlsen	17/23 (74%)	18/25 (72%)	1.03 (0.73-1.45)
Becker	41/58 (71%)	13/21 (62)%	1.14 (0.79-1.66)
Chaussade	41/60 (68%)	19/27(70%)	0.97(0.72-1.31)
Marculescu		18/55(33%)	
Brandt		12/33(36%)	
Lora-Tamayo 2016	41/63 (65%)		
Wouthuyzen-Bakker 2018	51/58 (88%)		
Barberan	39/60 (65%)		
Tschudin-Sutter	73/81(90%)		
Jacobs	44/56(79%)		
Cobo	35/57(61%)		
Fink	35/49(71%)		
Parvizi	13/35 (25%)		
Aboltins	18/20 (90%)		
Soriano	19/25 (76%		
Scheper	26/41 (63%)		
Letouvet	12/24(50%)		
Total hip+knee PJI	**903/1298 (70%)**	**186/354 (53%)**	**1.32 (1.19-1.47)**
Total	**1061/1490 (71%)**	**231/422 (55%)**	**1.30 (1.86-1.43)**

DAIR: debridement, antibiotics, implant retention
PJI: prosthetic joint infection

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