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REVIEW

Outcomes of culture-negative or -positive periprosthetic joint infections: A systematic review and meta-analysis

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ABSTRACT

Objectives: This study overviewed the current database of studies on periprosthetic joint infections (PJIs) to compare outcomes and antibiotic side effects in culture-negative or culture-positive PJIs and assess treatment options for culture-negative PJIs.

Materials and methods: A systematic review and meta-analysis was undertaken using studies published before July 2022 in MEDLINE, EMBASE, and Cochrane Library. All studies comparing treatment of culture-negative or -positive PJIs were included. Afterward, the infection control rate, periprosthetic or spacer fracture, hip joint or spacer dislocation, and antibiotic side effects in different treatment methods of PJI were analyzed.

Results: Eleven studies involving 1,747 patients were included. Most studies clearly defined the infection control criteria: no pain or swelling, no wound drainage, normal serology, and normal radiographic findings. Patients were followed until treatment failure, death, or until the last clinical visit without evidence of treatment failure. The two types of PJIs did not differ significantly in infection control rates (culture-negative PJI 79.2% *vs*. culture-positive PJI 76.6%; odds ratio [OR]=1.20, 95% confidence interval [CI]: 0.84 to 1.70), either after all types of surgical treatment or after two-stage revision arthroplasty (OR=1.12, 95% CI: 0.72 to 1.75), single-stage revision arthroplasty (OR=0.51, 95% CI: 0.19 to 1.37), or debridement, antibiotics, and implant retention (OR=0.88, 95% CI: 0.50 to 1.54). Similarly, we did not find differences in periprosthetic or spacer fracture and hip joint or spacer dislocation. For culture-negative PJIs, the infection control rate was 85.2% after two-stage revision arthroplasty, 90.6% after single-stage revision arthroplasty, and 69.7% after debridement, antibiotics, and implant retention. Data pooled from three studies showed higher incidence of antibiotic side effects for culture-negative PJIs.

Conclusion: The clinical outcomes of one-stage revision and two-stage revision are comparable. Therefore, both of them can be considered in surgical treatment for culture-negative PJIs. In addition, limited data showed a higher incidence of antibiotic side effects in culture-negative PJIs.

Keywords: Arthroplasty, culture, infection, joint, meta-analysis, outcome.

Total joint arthroplasty is frequently performed in patients with end-stage joint diseases, and despite the investment in stratified preventative measurements, prosthetic joint infection (PJI) remains the most frequent cause of early total joint arthroplasty failure.[1] The incidence of such infections is projected to rise in the future as a result of increased implantations and longer lifespans, translating to longer prosthesis retention.[1,2]

Identifying the infecting microorganism in PJI is critical for ensuring appropriate management.[3] Although various strategies have been implemented to improve positive culture rates,[4-7] recent literature reported that the prevalence of culture-negative PJI ranges between 9 and 42%.[8-11] If the bacteria cannot

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be identified, the choice of surgical treatment and antibiotics is a significant challenge.

Although two-stage revision arthroplasty is the preferred surgical approach for culture-negative PJIs,[12] several new options for the procedure have been proposed, such as single-stage revision arthroplasty and debridement, antibiotics, and implant retention (DAIR).[13-15] Although DAIR was once contraindicated for culture-negative PJIs, its application within four weeks can be effective against acute cases.[15]

Choosing antibiotics for the treatment of culture-negative PJI is difficult since the bacteria must be sensitive to the drug selected, yet long-term use of broad-spectrum antibiotics or multiple antibiotics against the most common infecting organisms is associated with the generation of resistances and carries risk of toxicity.[16]

The lack of knowledge on optimal treatment of culture-negative PJIs is coupled with the poor understanding of the prognosis. A greater understanding of the outcomes of culture-negative PJIs might help clinicians make better treatment choices.

This study aimed to *(i)* evaluate whether culture-negative PJI has worse outcomes than culture-positive PJI, *(ii)* compare the incidence of antibiotic side effects between culture-negative or -positive PJI, and *(iii)* compare the effects of different treatment options for culture-negative PJI.

MATERIALS AND METHODS

This systematic review and meta-analysis was conducted according to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) and Cochrane collaboration guidelines (Figure 1).

Search strategy and eligibility criteria

The authors conducted a systematic review search of studies about culture-negative PJIs in MEDLINE, EMBASE, and Cochrane Library databases published before July 2022. The following key search terms were used: "knee," "hip," "joint," "arthroplasty," "periprosthetic," "infection," and "culture." The search was restricted to publications in English.

Studies about periprosthetic infections of the hip and knee were included, while periprosthetic infections of other joints were excluded. Case reports, opinions of experts, unpublished data, instructional courses, review articles, and letters to the editors were excluded. Studies that lacked duration of follow-up, outcome data, and clear diagnostic criteria for PJI

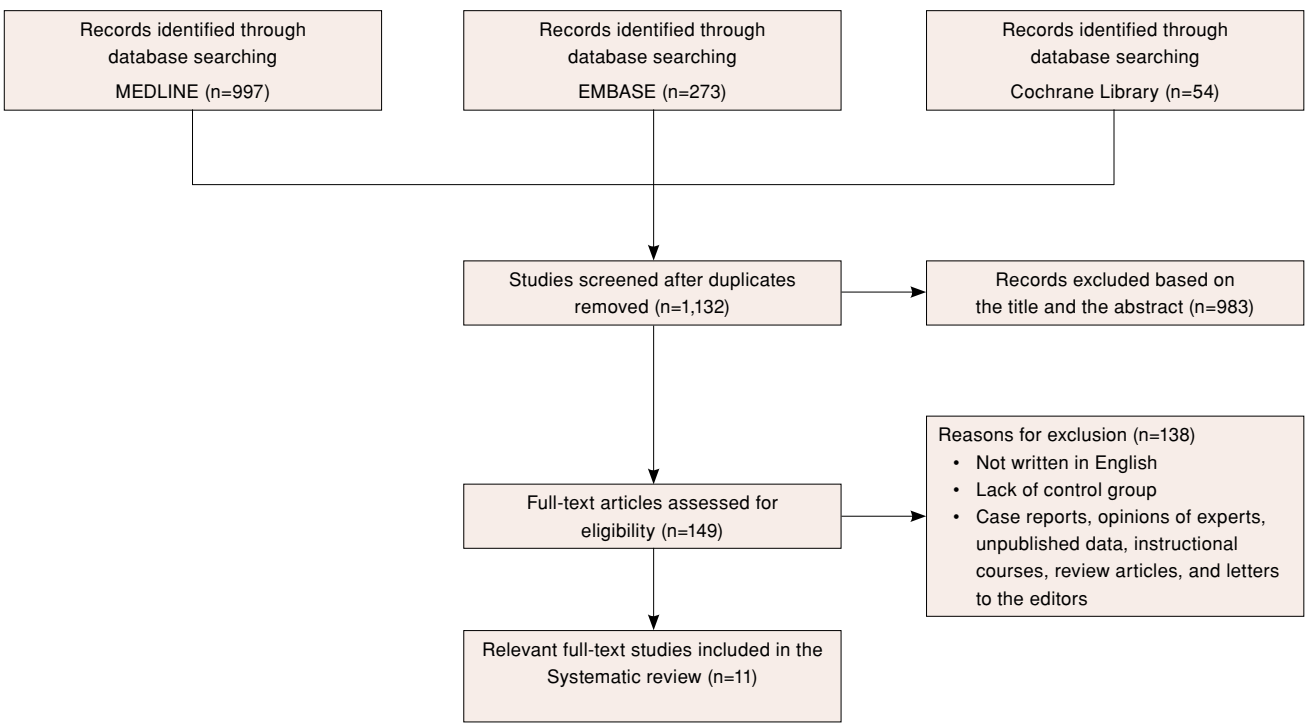


FIGURE 1. Flow diagram of the literature search and study inclusion.

TABLE I

Characteristics of studies included in the meta-analysis

Study	Location	Study design	Treatment interval	Surgery	Definition of PJI	Total number of cases	Prevalence of CN PJI cases %	Hip %	Knee %	Main observations
Greenfield et al.[21]	Manchester, UK	R	2006-2015	Single-stage revision	MSIS (2011)	105	73.3	100	-	Identification of the infecting organism before surgery did not influence the outcome
Ji et al.[19]	Xinjiang, China	R	2009-2016	Single-stage revision	McPherson et al.[49]	243	21.0	42.8	57.2	Single-stage revision with direct intra-articular antibiotic infusion can be effective in treating CN PJI and can achieve an infection control rate similar to that in CP PJI patients.
Tirumala et al.[15]	Boston, USA	R	NR	DAIR	ICM (2018)	149	30.9	39.6	60.4	DAIR with modular component exchange was associated with similar reinfection rates for acute CN or CP PJI
Ibrahim et al.[20]	London, UK	R	2007-2012	Two-stage revision	Berbari et al.[9]	100	50.0	100	-	Patients with CP or CN PJI after total hip arthroplasty can be treated effectively using two-stage revision and strict protocols as if they were complex CP patients
Santoso et al.[21]	Sebelas Maret University, Solo, Indonesia	R	2010-2015	Two-stage revision	MSIS (2011)	84	30.9	100	-	Two-stage revision resulted in comparable outcomes for CN or CP PJI of the hip
Wang et al.[22]	Shanghai, China	R	2003-2016	Two-stage revision	Parvizi et al.[29]	58	32.8	100	-	Two-stage revision can successfully treat PJI, with comparable outcomes for CN or CP PJI.
Li et al.[23]	Beijing, China	R	2003-2014	Single- and two-stage revision	MSIS (2011)	127	14.2	-	100	With combined or broad-spectrum antibiotics, CN and CP reinfection rates at 5 years were similar after total knee arthroplasty and two-stage revision.
Kim et al.[24]	Seoul, Korea	R	1991-2008	DAIR and two-stage revision	McPherson et al.[49]	191	26.7	-	100	Treatment according to the type of infection after total knee arthroplasty controlled infection and maintained knee function with firm fixation in most CP and CN patients.
Choi et al.[25]	Boston, USA	R	2000-2009	NR	MSIS (2011)	175	22.9	55.4	44.6	There were no differences in outcomes between CN and CP groups
Huang et al.[26]	Philadelphia, USA	R	2000-2007	DAIR and two-stage revision	MSIS (2011)	343	9.9	NR	NR	Aggressive two-stage exchange arthroplasty and postoperative parenteral vancomycin therapy achieved similar rates of infection-free survival in patients with CN or CP PJI.
Malekzadeh et al.[27]	Salzburg, Austria	R	1985-2000	DAIR and two-stage revision	Malekzadeh et al.[27]	270	-	50.4	49.6	Physicians should always consider the risk of a negative culture if they prescribe an antimicrobial therapy for a presumed infection, especially in settings where the therapy is unlikely to be effective.

PJI: Periprosthetic joint infection; CN: Culture-negative; CP: Culture-positive; MSIS: Musculoskeletal Infection Society; ICM: International Consensus Meeting; DAIR: Debridement, antibiotics, and implant retention; NR: Not reported; R: Retrospective.

TABLE II
Quality assessment of studies included in the meta-analysis

Study	Pre-intervention		At intervention		Post-intervention		Total	
	Bias due to confounding	Bias in participant selection	Bias in classification of interventions	Bias due to deviations from intended interventions	Bias due to missing data	Bias in measurement of outcomes	Bias in selection of reported result	Bias across domains
Greenfield et al.[18]	Moderate	Low	Moderate	Moderate	Low	Moderate	Moderate	Moderate
Ji et al.[19]	Low	Moderate	Low	Low	Low	Moderate	Moderate	Low
Tirumala et al.[15]	Low	Moderate	Low	Moderate	Low	Moderate	Low	Low
Ibrahim et al.[20]	Low	Moderate	Low	Moderate	Moderate	Moderate	Low	Moderate
Santoso et al.[21]	Moderate	Moderate	Low	Moderate	Serious	Moderate	Moderate	Moderate
Wang et al.[22]	Low	Low	Low	Moderate	Low	Moderate	Moderate	Low
Li et al.[23]	Low	Low	Low	Moderate	Serious	Low	Low	Moderate
Kim et al.[24]	Low	Moderate	Moderate	Moderate	Moderate	Low	Moderate	Low
Choi et al.[25]	Moderate	Moderate	Moderate	Moderate	Moderate	Serious	Moderate	Moderate
Huang et al.[26]	Moderate	Moderate	Moderate	Serious	Moderate	Moderate	Moderate	Moderate
Malekzadeh et al.[27]	Moderate	Low	Low	Moderate	Moderate	Moderate	Moderate	Moderate

were also excluded. In addition, studies that only included a culture-negative PJI cohort were excluded since lack of contrast for culture-positive PJI may cause our results to be unreliable. The titles and abstracts of the selected studies were screened by two of the authors. If they found the titles and abstracts to be relevant, the full text was evaluated to determine whether the study could be included. Disagreements were resolved by discussion between the two authors.

Data extraction

Two authors independently extracted relevant data from the included studies (Table I). Extracted outcomes included the incidence of culture-negative PJI, total infection control rate, infection control rate after two-stage revision arthroplasty, single-stage revision arthroplasty, or DAIR, periprosthetic or spacer fracture rate, hip joint or spacer dislocation rate, and complication rates due to antibiotics. Most studies clearly defined the infection control criteria: no pain or swelling, no wound drainage, normal serology, and normal radiographic findings. All patients were followed until treatment failure, death, or until the last clinical visit without evidence of treatment failure. The minimum follow-up period of the patients without recurrent infection was two years. As most of the studies we included did not report hip and knee outcomes in subgroups, we were unable to perform subgroup analyses after data extraction, which may need to be supplemented by more studies.

Statistical analysis

Review Manager version 5.4 from the Cochrane Collaboration (https://training.cochrane.org/online-learning/core-software-cochrane-reviews/revman) was used to analyze extracted data. Results were reported as odds ratios (ORs) and 95% confidence intervals (CIs). Heterogeneity across studies was assessed using the chi-squared test and I^2 statistic. We considered heterogeneity small when I^2 was equal to 0, using a fixed-effect model; otherwise, we used a random-effects model.

Quality assessment

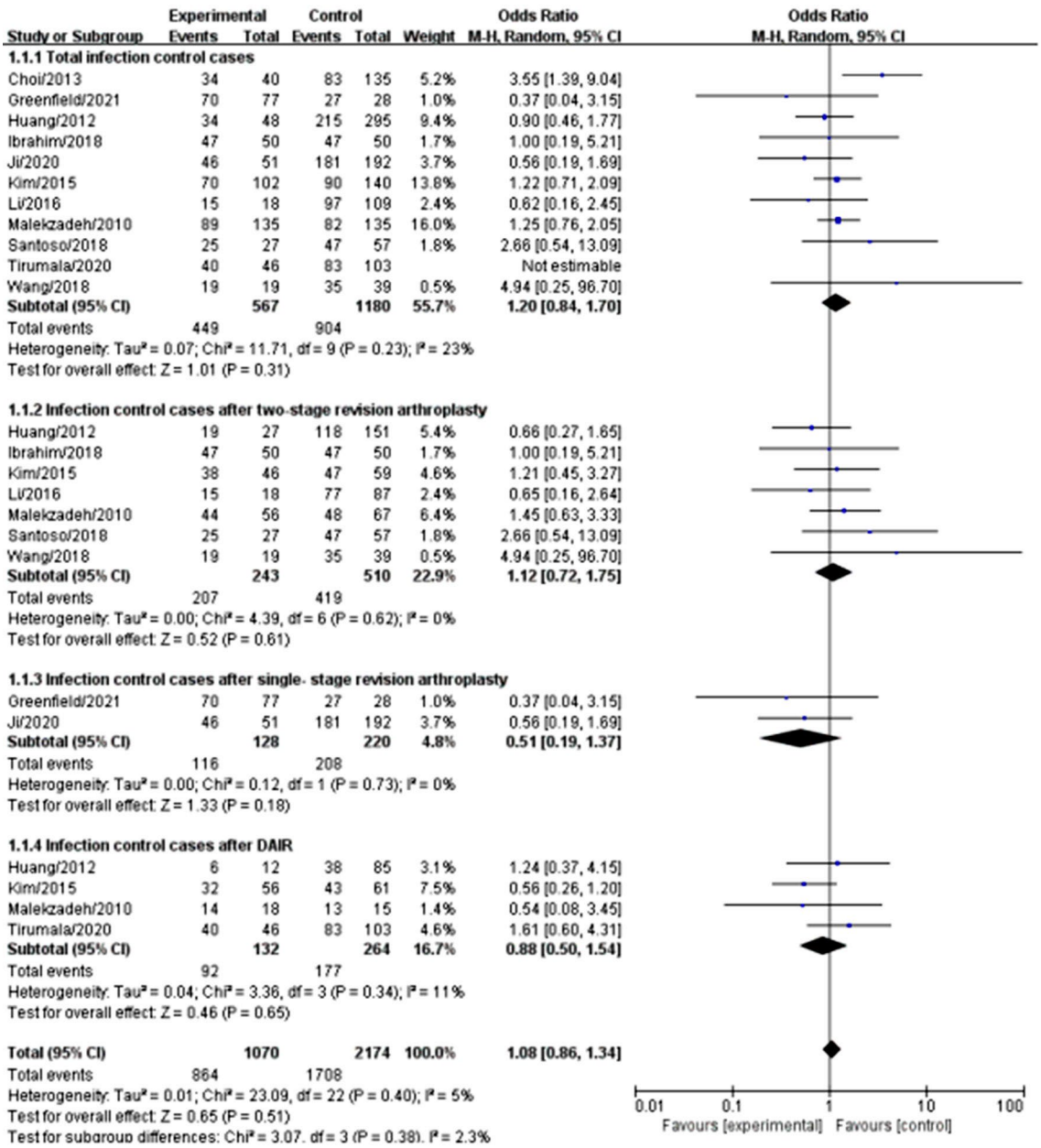
The risk of bias in the included studies was evaluated using the ROBINS-I (risk of bias in nonrandomized studies of interventions; https://sites.google.com/site/riskofbiastool/welcome/home?authuser=0) evaluation tool[17] from the Cochrane Collaboration (Table II). The risk of bias in each study was classified as "low," "moderate," "severe," "critical," or "no information."[17] Two authors performed bias evaluations independently.

In case of disagreement, the authors reached consensus through discussion.

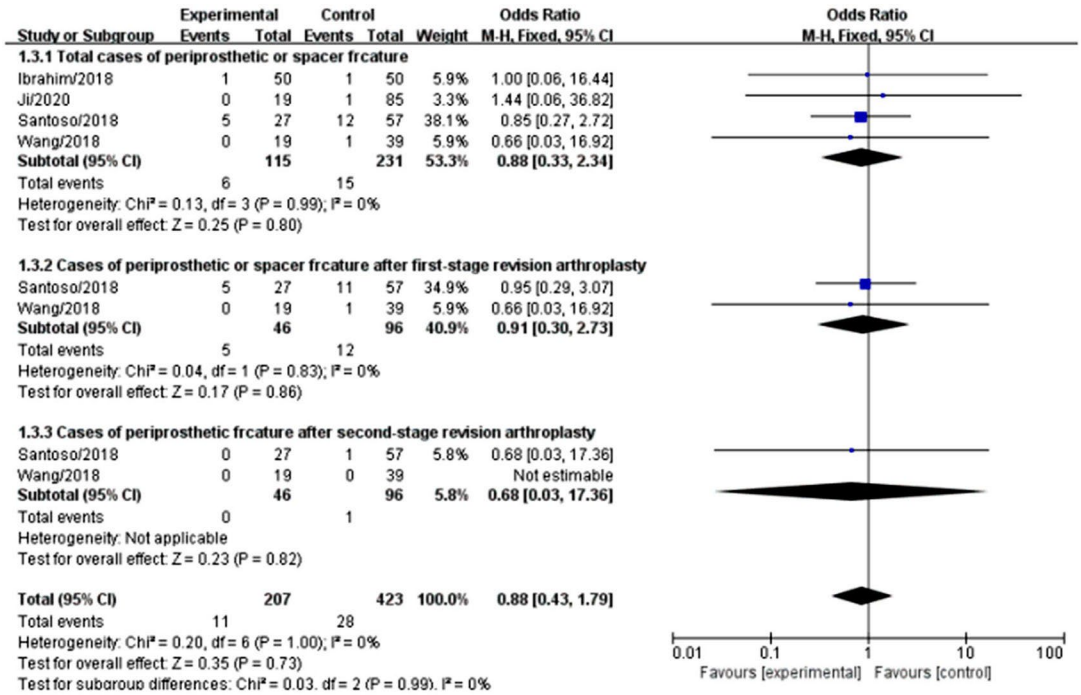
RESULTS

A total of 1,324 results were retrieved, of which 997 were from MEDLINE, 273 from EMBASE, and 54 from Cochrane Library. One hundred ninety-two duplicate studies and another 983 studies were excluded after reviewing the titles and abstracts. Finally, 11 studies involving 1,747 patients were included in the systematic review and meta-analysis (Figure 1, Table I).[15,18-27] All studies were retrospective and were published between 2010 and 2022. Of the 1,747 patients, 567 (32.5%) had culture-negative PJIs. The incidence of culture-negative PJI ranged from 9.9 to 73.3% across the included studies. Overall, the quality of the included studies was unsatisfactory. Four studies[15,19,22,24] were considered to have moderate risk of bias, and seven studies[18,20,21,23,25-27] were at significant risk of bias, which could be due to their retrospective nature. In most studies, PJI was diagnosed based on the 2011 Musculoskeletal Infection Society (MSIS) criteria. Five studies[19,20,22,24,27] applied other diagnostic criteria (Table I).

(a)



(b)



(c)

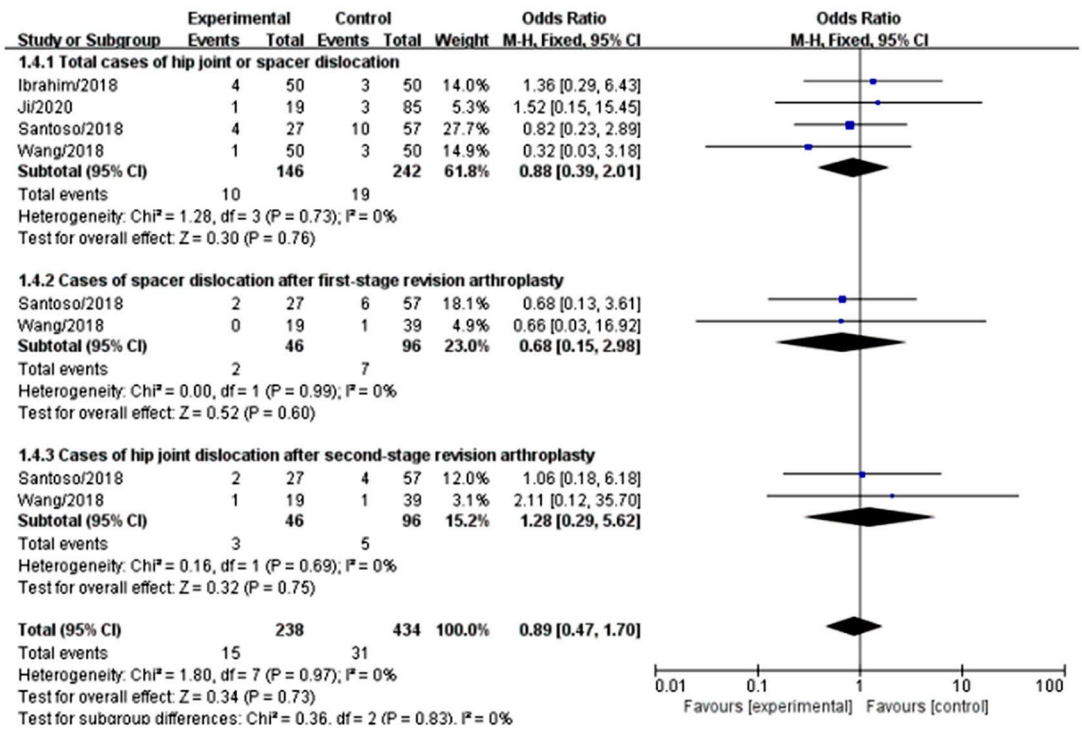


FIGURE 2. (a) Forest plots of meta-analysis of culture-negative periprosthetic joint infection (experimental group) *vs.* culture-positive periprosthetic joint infection (control group) in a) infection control rate and b) periprosthetic or spacer fracture rate. **(b)** Forest plots of meta-analysis of culture-negative periprosthetic joint infection (experimental group) *vs.* culture-positive periprosthetic joint infection (control group) in a) infection control rate and b) periprosthetic or spacer fracture rate. **(c)** Forest plots of meta-analysis of culture-negative periprosthetic joint infection (experimental group) *vs.* culture-positive periprosthetic joint infection (control group) in a) infection control rate and b) periprosthetic or spacer fracture rate.

The most common surgical intervention was two-stage revision arthroplasty, with 753 patients (43.1%), while 348 (19.9%) underwent single-stage revision arthroplasty, and 396 (22.7%) underwent DAIR. The remaining 250 patients (14.3%) underwent other surgical procedures, or the surgical procedure was not reported. After surgery, most culture-negative PJIs were managed with intravenous vancomycin, which in some cases was supplemented with cephalosporin, ciprofloxacin, or other antibiotics.

Infection control rates for all included studies were defined as the number of patients free from PJI recurrence or the total number of patients in the cohort. All but one of the included studies reported similar infection control rates for culture-negative or -positive PJIs. One study reported higher infection control rates for culture-negative PJIs (culture-negative PJI 85% *vs.* culture-positive PJI 61%, p=0.006).[25] Across all studies, the total infection control rate was 79.2% for culture-negative PJIs and 76.6% for culture-positive PJIs (OR=1.20, 95% CI: 0.84 to 1.70). Infection control rates did not differ significantly between culture-negative or -positive PJIs when all treatments were considered together or when they were considered individually: two-stage revision arthroplasty (culture-negative PJI 85.2% *vs.* culture-positive PJI 85.2%, OR=1.12, 95% CI: 0.72 to 1.75), single-stage revision arthroplasty (90.6% *vs.* 94.5%, OR=0.51, 95% CI: 0.19 to 1.37), or DAIR (69.7% *vs.* 67.0%, OR=0.88, 95% CI: 0.50 to 1.54; Figure 2a). Similarly, no differences were observed between culture-negative or -positive PJIs in terms of periprosthetic or spacer fracture (4.0% *vs.* 6.5%, OR=0.88, 95% CI: 0.33 to 2.34, Figure 2b) or in terms of hip joint or spacer dislocation (6.8% *vs.* 7.9%, OR=0.88, 95% CI: 0.39 to 2.01, Figure 2c).

Three studies reported rates of antibiotic-related complications, including nephrotoxicity, hepatotoxicity, and gastrointestinal toxicity. One study reported the incidence of antibiotic complications to be 8% for culture-negative PJI and 2% for culture-positive PJI.[27] Another reported the corresponding rates to be 5.9% and 0%.[19] A third study reported much higher incidence of 55.6% for culture-negative PJI.[23]

DISCUSSION

Although the MSIS and the International Consensus Meeting (ICM) continue to improve the criteria for standardizing the definition of PJI,[28-30] its diagnosis poses a significant challenge in clinical work, particularly when the causative pathogen is unclear. The high incidence of culture-negative PJI in our meta-analysis was 32.5%, which highlights the need to standardize diagnostic protocols and optimize treatment recommendations. Previous systematic reviews of culture-negative PJI focused on its diagnosis, improvement of bacterial culture rates, and treatment modalities.[4,31] However, to date, we have found no previous systematic review focusing on infection control rate and other possible causes of reoperation of culture-negative PJI.

In our meta-analysis, we found that infection control rates, either for all surgical treatments or for particular ones, did not differ significantly between culture-negative or -positive PJIs. However, one study excluded from our systematic review on the basis of the exclusion criteria found that culture-negative PJI is a relatively frequent finding with unacceptable rates of treatment failure (30.8%).[32] Unfortunately, that study did not include culture-positive PJIs as a control group. Those investigators emphasized the need to isolate the infecting organism before surgical intervention.

Most of the included studies agreed that there was no difference in the infection control rates between culture-positive or -negative PJIs. The only exception was one publication that suggested a higher infection control rate in the culture-negative PJI group.[25] The authors attributed the higher rate to previous treatment with antibiotics or surgery and to the use of vancomycin, reimplantation, and arthrodesis.

In view of the results of our meta-analysis, we consider that culture-negative PJI has an infection control rate comparable to that of culture-positive PJI. One reason may be surgeons' greater caution regarding lesion clearance. Second, when the causative bacteria are unknown, surgeons may prefer long-term use of broad-spectrum or next-generation antibiotics. Third, the culture-negative PJIs in most studies may involve bacteria of lower virulence than culture-positive PJIs, which may involve, for example, methicillin-resistant Staphylococcus aureus.[33]

In addition to reinfection, another thorny problem is periprosthetic or spacer fracture and hip joint or spacer dislocation, as these complications are likely to necessitate reoperation. However, the incidence of these complications did not differ significantly between culture-negative or -positive PJIs in our systematic review.

Treatment of PJI usually involves surgical treatment and antibiotics. Existing mainstream surgical treatment modalities mainly include two-stage revision arthroplasty, single-stage

revision arthroplasty, and DAIR. Previous studies have shown that when infection has been established but the bacteria cannot be cultured, two-stage revision arthroplasty is preferred, and it can reach an eradication rate of 90%.[20,34] This strategy allows for a second attempt at debridement and an opportunity to obtain microbiological samples; the interval also allows the assessment of the response to antibiotics.[19] However, staged procedures require patients to undergo two or even more procedures over a short period, which can increase patient burden and health care costs, as well as cause significant morbidity and mortality.[35] Recently, a study found no difference in infection control rates between two or single-stage revision arthroplasty in the treatment of culture-negative PJI.[36] Other work suggested that single-stage revision arthroplasty with direct intra-articular antibiotic infusion may achieve a similar infection control rate for culture-negative PJI as for culture-positive PJI and may reduce the systemic side effects of antibiotics, allowing higher local drug concentrations.[19] Another study demonstrated that DAIR involving modular component exchange was associated with similar reinfection rates for acute culture-negative or -positive PJIs.[15]

Interestingly, our systematic review and meta-analysis found even higher infection control rates with single-stage revision arthroplasty than with two-stage revision arthroplasty, while the infection control rate of acute PJI (<4 weeks) with DAIR was not satisfactory. One caveat is that contraindications to single-stage revision arthroplasty include an immunocompromised host, severe soft tissue or bone defects, or intercurrent acute sepsis.[37] However, in the chronic PJI (>4 weeks) setting, single-stage revision arthroplasty has been contraindicated in cases of culture negativity,[38] in which two-stage revision arthroplasty is preferred and surgeons are reluctant to risk using single-stage revision arthroplasty substitutions.

Based on our systematic review, we consider that the high infection control rate in culture-negative PJI is strongly associated with the routine use of vancomycin. In some of the included studies, use of vancomycin was associated with use of cephems or even meropenem. Antibiotic selection for culture-positive PJI is not a difficult task, but it remains challenging for culture-negative PJI. The 2018 ICM recommendations state that "in patients with true culture-negative-PJIs, antibiotics should be selected to have broad spectrum activity against both Gram-positive and Gram-negative organisms. In addition, the exact choice should relate to the known modern epidemiology in that country."[39] Currently, vancomycin is the antibiotic used to treat most PJI patients after surgery, either alone or in combination with other antibiotics. Indeed, vancomycin was most frequently used in our included studies, and in some studies, it was combined with cephalosporins or other local empirical antibiotics. Vancomycin use might be associated with higher infection control rates in culture-negative PJI as it is particularly effective against gram-positive species that form biofilms, such as Staphylococcus, Streptococcus, and Enterococcus.[40] One study identified Staphylococcus as the offending organism in >50% of their culture-negative reinfections.[41]

On the other hand, vancomycin and other broad-spectrum antibiotics can cause greater systemic side effects than narrow-spectrum antibiotics used after drug sensitivity experiments. These side effects include nephrotoxicity, hepatotoxicity, gastrointestinal toxicity, allergic reactions, and multidrug resistance.[42,43] These side effects add to the complications of treating culture-negative PJIs. One study reported that 11 of 135 patients with culture-negative PJI (culture-negative 8% *vs.* culture-positive PJI 2%) developed an adverse reaction to systemic antimicrobial therapy.[27] Another study found that 10 (55.6%) of 18 culture-negative PJIs suffered antibiotic treatment-related side effects.[23] A subsequent study recorded two cases of impaired renal function and one local adverse reaction in the culture-negative group after treatment with vancomycin and a direct intra-articular infusion of imipenem (culture-negative PJI 5.9% *vs.* culture-positive PJI 0%).[19]

There has been increasing interest in the use of topical vancomycin in recent years.[44-46] Delivery of antibiotics directly to the target area allows for high local drug concentrations while potentially limiting side effects.[47] In a systematic review of nine studies involving 4,607 patients, intrawound vancomycin was associated with lower incidence of PJI and simultaneous acute kidney injury in primary total joint arthroplasty.[48] Since the local use of vancomycin during this procedure can effectively reduce the incidence of antibiotic-related complications, it may do the same for revision arthroplasty of PJI. One study reported that the addition of intraosseous vancomycin at the time of DAIR was safe and that it gave better results than standard DAIR without intraosseous antibiotic administration.[46] However, strong evidence for this conclusion is lacking since

most of the studies in the present systematic review are low-quality retrospective studies, and doses of vancomycin vary. In addition, most studies regarding the local use of vancomycin have been limited to primary total joint arthroplasty, and few studies have investigated the local use of vancomycin in PJI. More high-quality randomized clinical trials are needed to verify the safety and efficacy of topical vancomycin in PJI.

Given that the studies on culture-negative PJI in our review were all retrospective, the greatest limitation of our review and meta-analysis is the low study quality. In addition, the included studies varied in their definitions of culture-negative PJI, potentially leading to some bias in the inclusion criteria. However, after reviewing the definition of culture-negative PJI for each of the included studies, we do not think that the variation in diagnostic criteria substantially affected our results. Finally, there are few studies comparing single-stage revision arthroplasty, two-stage revision arthroplasty, and DAIR, thus the best treatment of culture-negative PJI remains unclear. Therefore, there is a need for more prospective randomized clinical trials to determine whether culture-negative PJI has the same outcomes as culture-positive PJI and to explore the optimal treatment modalities for culture-negative PJI, including the antibiotic used, dose, time, and choice of surgical treatment.

In conclusion, the meta-analysis did not find differences between culture-negative and -positive PJI in rates of infection control, periprosthetic or spacer fracture, or hip or spacer dislocation. For the treatment of culture-negative PJI, two-stage revision arthroplasty and single-stage revision arthroplasty showed similar outcomes. Considering the side effects of broad-spectrum antibiotic use, as well as economic issues, greater efforts should be directed at improving the bacterial culture positivity rate.

Data Sharing Statement: The data that support the findings of this study are available from the corresponding author upon reasonable request.

Author Contributions: Idea/concept, design: Z.Z., Y.L., H.X.; Control/supervision, references and fundings: Z.Z.; Data collection and/or processing: X.L., W.Z.; Analysis and/or interpretation: X.L., N.L.; Literature review: Y.L., H.X.; Writing the article: Y.L.; Critical review: H.X.; Materials: Y.L., H.X.

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