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**Prosthetic joint infection of the hip and knee due to *Mycobacterium* species: A systematic review**

Santoso A *et al.* Hip and knee PJI due to *Mycobacterium*

## Abstract

### BACKGROUND

*Mycobacterium species* (*Mycobacterium sp*) is an emerging cause of hip and knee prosthetic joint infection (PJI), and different species of this organism may be responsible for the same.

### AIM

To evaluate the profile of hip and knee *Mycobacterium* PJI cases as published in the past 30 years.

### METHODS

A literature search was performed in PubMed using the MeSH terms “Prosthesis joint infection” AND “Mycobacterium” for studies with publication dates from January 1, 1990, to May 30, 2021. To avoid missing any study, another search was performed with the terms “Arthroplasty infection” AND “Mycobacterium” in the same period as the previous search. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses chart was used to evaluate the included studies for further review. In total, 51 studies were included for further evaluation of the cases, type of pathogen, and treatment of PJI caused by *Mycobacterium sp*.

### RESULTS

Seventeen identified *Mycobacterium spp.* were reportedly responsible for hip/knee PJI in 115 hip/knee PJI cases, whereas in two cases there was no mention of any specific *Mycobacterium sp*. *M. tuberculosis* was detected in 50/115 (43.3%) of the cases. Nontuberculous mycobacteria (NTM) included *M. fortuitum* (26/115, 22.6%), *M. abscessus* (10/115, 8.6%), *M. chelonae* (8/115, 6.9%), and *M. bovis* (8/115, 6.9%). Majority of the cases (82/114, 71.9%) had an onset of infection > 3 mo after the index surgery, while in 24.6% (28/114) the disease had an onset in ≤ 3 mo. Incidental intraoperative PJI diagnosis was made in 4 cases (3.5%). Overall, prosthesis removal was needed in 77.8%

(84/108) of the cases to treat the infection. Overall infection rate was controlled in 88/102 (86.3%) patients with *Mycobacterium* PJI. Persistent infection occurred in 10/108 (9.8%) patients, while 4/108 (3.9%) patients died due to the infection.

## CONCLUSION

At least 17 *Mycobacterium* spp. can be responsible for hip/knee PJI. Although *M. tuberculosis* is the most common causal pathogen, NTM should be considered as an emerging cause of hip/knee PJI.

**Key Words:** *Mycobacterium* species; Prosthetic joint infection; Hip; Knee; Systematic review

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**Core Tip:** Prosthetic joint infection (PJI) is a difficult complication after total hip/knee arthroplasty. *Mycobacterium* species is one of the emerging causes of hip and knee PJI, and various species could be responsible for it. This study aimed to evaluate the profile of hip and knee *Mycobacterium* PJI cases published in the past 30 years. This study resulted the information regarding the distribution of *Mycobacterium* species that related to PJI hp/knee. This paper also evaluated the disease course, treatment and outcome of *Mycobacterium* PJI.

## INTRODUCTION

The incidence of prosthetic joint infection (PJI) has increased with an increase in the number of patients undergoing total joint arthroplasty, particularly hip and knee arthroplasties<sup>[1]</sup>. The cumulative incidence of PJI after total hip arthroplasty (THA) and total knee arthroplasty remains unclear; however, it is believed to range between 2.05%

and 2.18%. The majority of PJI cases<sup>2</sup> are caused by gram-positive cocci such as *Staphylococcus aureus* and coagulase-negative *Staphylococci* (60%); however, sometimes they can also be caused by gram-negative bacteria, such as *Mycobacteria* or fungi<sup>[2,3]</sup>. *Mycobacterial* infections account for approximately 2% of all PJI cases<sup>[4]</sup>. *M. tuberculosis* is an infrequent cause of PJI, accounting for only 7 cases (0.3%) as reported during a 22-year period at one center<sup>[5]</sup>. However, in tuberculosis-endemic countries, patients undergoing joint arthroplasty with previous tuberculous septic arthritis are at an increased risk of developing *M. tuberculosis* complex PJI<sup>[1]</sup>. Some other *Mycobacteria* (rapidly growing *Mycobacteria*) are reported to grow rapidly, and they spread in various environments worldwide<sup>[4]</sup>.

Appropriate management is mandatory to prevent complications that arise from PJI. Successful management of PJI is achieved by a combination of surgical intervention and appropriate medical therapeutic strategies to eradicate infection, reduce pain, restore function, and prevent prolonged antimicrobial therapy in patients<sup>[1,2,6]</sup>. The diagnosis of mycobacterial infections is often delayed due to the low index of suspicion, clinical and laboratory presentation that mimics bacterial infections, and low yield of smears and culture for acid-fast bacilli. Moreover, mycobacterial infections are often known to occur together with other bacteria, such as coinfection or superinfection<sup>[2,6]</sup>. Delayed diagnosis and prevention of PJI can lead to prolonged illness with various dangerous manifestations that can threaten the patient's life. Although *Mycobacteria* are not among the common causative agents of PJI, it is important to recognize and treat them differently from non-mycobacterial infections. The aim of this study was to identify and evaluate the profile of PJI cases due to mycobacterial infection in the hip and knee as published over the past 30 years.

## **MATERIALS AND METHODS**

### ***Search strategy***

A literature search was performed using MeSH terms on PubMed from January 1, 1990, to May 30, 2021. The following two search scenarios were used accordingly: "Prosthesis

joint infection AND Mycobacterium,” and “Arthroplasty infection AND Mycobacterium.” The articles were screened based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement.

### ***Inclusion and exclusion criteria***

The following inclusion criteria were used in our systematic review: (1) Clinical studies; (2) All levels of evidence; and (3) PJI of the hip or knee due to any *Mycobacterium species*. Studies were excluded if they met any of the following criteria: (1) Non-English articles; (2) PJI not involving the hip or knee joint; (3) Primary *Mycobacterium* hip/knee osteoarticular infection prior to arthroplasty; (4) Articles published in abstract form only; (5) Review articles; and (6) Technique articles.

### ***Data collection/extraction***

Three authors (Santoso A, Phatama KY, and Rhatomy S) independently screened the titles and abstracts of the included studies. The first search with the terms “Prosthetic joint infection AND Mycobacterium” revealed 54 records. Of these, 6 records were excluded for not being in English, 5 for presenting primary osteoarticular hip/knee infection, 2 for presenting shoulder/elbow PJI, 1 for presenting wound infection after THA without involvement of the joint, and 3 for unavailability of the full-text articles. The remaining 37 records were included in the further analysis. The second search method was performed with the words “Arthroplasty infection AND Mycobacterium,” which revealed 56 records. Of these, 33 records were excluded for duplicating previous search results, 4 for presenting primary hip/knee osteoarticular infection, 1 for presenting shoulder PJI, 1 for being a non-English article, 2 for being review articles, and 1 for unavailability of the full-text article. Thus, 14 records were finally included from the second search in the analysis. Considering the 37 records from the first search and 14 from the second search, a total of 51 records were included in the final analysis (Figure 1). The analysis included type of study, demographics, number of patients, hip or knee PJI cases, *Mycobacterium sp.* strain, treatment, and outcomes of the

mycobacterial PJI cases (Table 1). Furthermore, we performed a descriptive comparison between PJI caused by *M. tuberculosis* ( $n = 43$ ) and *nontuberculous mycobacteria* (NTM) ( $n = 63$ ). This comparative evaluation excluded all cases of mixed infections of *M. tuberculosis* and NTM ( $n = 1$ ), NTM and *Staphylococcus species* (*Staphylococcus sp.*) ( $n = 2$ ), and *M. tuberculosis* and *Staphylococcus sp.* ( $n = 6$ ). Two cases with no data regarding the specific species of *Mycobacteria* were also excluded at this stage (Table 2). Comparative analysis of categorical data was performed using the chi-square test.

## **RESULTS**

Of the 51 included studies, 40 (80.3%) were case reports and 11 (19.6%) studies were of the retrospective series type. There were studies from America (27/51, 52.9%), Europe (12/51, 23.5%), and Asia-Pacific (12/51, 23.5%) included in the analysis. In total, 117 *Mycobacterium* hip/knee PJI cases were reported across 51 studies. There were 46.15% (54/117) cases of knee PJI and 53.85% (63/117) of hip PJI, and the age range of the patients was 17-101 years. In total, 17 types of *Mycobacteria spp.* recorded in this review were responsible for PJI in 115 hip/knee PJI cases, whereas in 2 cases there was no mention of any specific *Mycobacterium sp.* *M. tuberculosis* was detected in 50/115 (43.3%) of the cases. The NTM included *M. fortuitum* (26/115, 22.6%), *M. abscessus* (10/115, 8.6%), *M. chelonae* (8/115, 6.9%), and *M. bovis* (8/115, 6.9%). Other strains with a smaller number of cases were also isolated as the causes of hip/knee PJI (Figure 2). Mixed infections in mycobacterial PJI cases were noted in 8 cases caused by *M. abscessus* and *M. fortuitum* (all NTM) in 1 case and by *M. tuberculosis* and *M. chelonae* in another. The other six cases showed co infection with *Staphylococcus sp.* The majority of the cases (82/114, 71.9%) showed an onset of infection > 3 mo after the index surgery, whereas 24.6% (28/114) of patients showed disease onset in  $\leq 3$  mo. Incidental intraoperative PJI diagnosis was reported in 4 cases (3.5%) (Figure 3), and it was not specified in 9 cases. Removal of the prosthesis (with or without revision) was needed in 77.8% (84/108) of cases to treat the infection (Figure 4). While debridement was needed in 11/108 (10.2%) cases, antimicrobial therapy was needed in 12/108 (11.1%), and amputation was

performed in 1 case. The overall infection rate was controlled in 88/102 (86.3%) *mycobacterial* PJI cases. Persistent infection occurred in 10/102 (9.8%) patients, and 4/102 (3.9%) patients died due to the infection (Figure 5). Comparative analysis showed no difference in the rate of hip or knee involvement in PJI with *M. tuberculosis* or NTM ( $P > 0.05$ ). Both *tuberculous* and *nontuberculous* PJI cases predominantly showed disease onset of  $> 3$  mo (79.1% and 63.3%, respectively). However, *nontuberculous* PJI cases showed a higher rate of early onset ( $< 3$  mo) of disease than those cases with tuberculous PJI (36.7% *vs* 11.6%). Removal of the prosthesis was needed in more cases of nontuberculous PJI than in cases of tuberculous PJI (88.9% *vs* 58.1%). The infection control rates were comparable between the tuberculous and nontuberculous PJI cases (81.4% and 91.7%, respectively) (Table 2).

## **DISCUSSION**

More than 150 *Mycobacterium* spp. have been officially recognized until now, in literature which consist of tuberculous mycobacteria and NTM<sup>[56]</sup>. One of the purposes of this systematic review was to evaluate the various *Mycobacteria* spp. that can cause hip/knee PJI, and at least 17 *Mycobacterium* spp. were identified accordingly. They comprised of *M. tuberculosis* and 16 NTM. The NTM was further divided into rapidly growing and slowly growing mycobacteria<sup>[56]</sup>. Several studies have reported rapidly growing NTM as the cause of early hip/knee PJI<sup>[4,17,18,28]</sup>. Early PJI ( $\leq 3$  mo) was noted in 36% of the NTM cases in this review, which was higher than that in tuberculous PJI cases (11%). The rapidly growing NTM hence needs to be considered as a differential diagnosis in cases of early hip/knee PJI. The diagnosis of *Mycobacterium* PJI is sometimes delayed, leading to delays in appropriate management<sup>[6,8]</sup>. Several treatment options were noted in this review. Removal of the prosthesis was the most commonly performed procedure, which was required in  $> 75\%$  of cases. Additionally, a greater number of NTM PJI cases required removal of the prosthesis compared to the tuberculous PJI cases (88.9% *vs* 58.1%). There were no data regarding specific procedures, such as revision surgery, resection arthroplasty, or arthrodesis after the



prosthesis removal procedure due to incomplete data in every published article. Another interesting finding was that conservative treatment with only antimicrobial therapy successfully controlled tuberculous hip/knee PJI in approximately 23% of the cases. This indicates that early recognition of sensitive antimicrobial agents is highly important in treating *Mycobacterium* PJI. However, the isolation of *Mycobacterium* with standard culture procedures may be sometimes difficult and more advanced techniques with gene sequencing are hence needed to isolate the *Mycobacterium sp*<sup>[19]</sup>. This could be a hindrance, especially in developing countries. Based on the pooled case analyses reported from the studies included in this systematic review, the outcome of the treatment of *Mycobacterium* PJI reportedly had an infection control rate of approximately 86%. Among the mycobacterial PJI cases, the infection control rate of nontuberculous PJI was comparable to that of tuberculous PJI (91.7% vs 81.4%,  $P = 0.092$ ). This was comparable to that of PJI hip/knee associated with non-mycobacterial pathogens or even a negative-culture PJI that showed an infection control rate of 70%-90%<sup>[3,57]</sup>. *Mycobacterium* PJI has also been correlated with culture-negative PJI. A study by Palan *et al*<sup>[58]</sup> reported that fungi and mycobacteria are responsible for over 85% of negative-culture PJI. Arthroplasty surgeons need to consider *Mycobacterium* as the causal pathogen of PJI when negative culture results are obtained in clinical practice. Further diagnosis using histopathology or polymerase chain reaction assay is needed accordingly.

This study had a few limitations. First, the systematic review only included studies indexed in PubMed; therefore, some other studies may have been missed in this review. However, the wider search period (30 years) of this systematic review ensured the inclusion of several important studies from literature. Second, <sup>1</sup>the studies included in this systematic review were mostly retrospective case reports or case series, which had their own limitations. It is difficult to obtain a higher level of evidence from relatively rare cases, such as those of *Mycobacterium* PJI. Third, some bias of treatment and outcome evaluation may have occurred, as every author may have used a different standard. This study also could not suggest any advisable best treatment for

<sup>3</sup>  
*Mycobacterium* PJI due to the lack of available data for evaluation. Despite these limitations, we believe that this systematic review could provide some insights into the profile of *Mycobacterium* hip/knee PJI, including its treatment options and outcomes.

## **CONCLUSION**

At least 17 *Mycobacterium spp.* can be responsible for PJI of the hip and knee. Although *M. tuberculosis* is the most common causal pathogen, NTM should be considered as an emerging cause of hip/knee PJI.

## **ARTICLE HIGHLIGHTS**

### ***Research background***

There were many species of *Mycobacterium* that may be associated as a causal pathogens for prosthetic joint infection (PJI) of the hip and knee. However, no available literature which provides compilation data regarding this issue.

### ***Research motivation***

To do compilation data of *Mycobacterium species (Mycobacterium sp)* which may cause hip and knee PJI.

### ***Research objectives***

This study aimed to evaluate PJI associated with *Mycobacterium sp.*

### ***Research methods***

Systematic review of PubMed article.

### ***Research results***

Among reviewed 51 articles. We found several species of *Mycobacterium* may be associated with hip and knee PJI.

### ***Research conclusions***

We found at least 17 species of *Mycobacterium* could be responsible for hip and knee PJI.

### ***Research perspectives***

This study may open the knowledge of various species of *Myscobacterium* that can be associated with hip and knee PJI.

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