Mycobacterium tuberculosis prosthetic joint infections a case series and literature review

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Mycobacterium tuberculosis prosthetic joint infections: a case series and literature review

Running title: *Mycobacterium tuberculosis* prosthetic joint infections

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ABSTRACT

*Objectives***:** We aimed to characterize diagnosis, management, and outcome of *Mycobacterium tuberculosis* prosthetic joint infections (PJI).

Methods: Cases of *M. tuberculosis* PJI documented in 7 referral French centers were retrospectively reviewed. Data were collected from medical files on a standardized questionnaire. We performed a literature review using the keywords 'prosthetic joint', and 'tuberculosis'.

Results: During years 1997-2016, 13 patients (8 males, 5 females, median age 79 years [range, 60-86]) had documented *M. tuberculosis* PJI, involving hip (n=6), knee (n=6), or shoulder (n=1). Median time from arthroplasty to diagnosis was 9 years [0.4-20]. The diagnosis was obtained on joint aspirates (n=9), or synovial tissue (n=4). PCR was positive in all cases tested (5/5). Median duration of antituberculosis treatment was 14 months [6-32]). Nine patients underwent surgery: debridement (n=4), resection arthroplasty (n=3), and revision arthroplasty (1-stage exchange, n=2). PJI was controlled in 12 patients. Seventeen additional cases of documented *M. tuberculosis* PJI have been reported, with a favorable outcome in 79% (11/14) of patients with no surgery, 85% (11/13) with debridement, 86% (19/22) with revision arthroplasty, and 81% (17/21) with resection (NS).

Conclusions: M. tuberculosis PJI can be controlled with prolonged antituberculosis treatment in most cases, with or without surgical treatment.

Keywords: Prosthetic joint; *Mycobacterium tuberculosis*; arthroplasty; debridement; antituberculosis drug.

Introduction

Mycobacterium tuberculosis is a rare cause of prosthetic joint infection (PJI), as most countries with high prevalence of tuberculosis have limited access to prosthetic arthroplasty. Moreover, as the diagnosis relies on specific tests not routinely performed for PJI, a significant proportion of *M. tuberculosis* PJI cases probably remain undiagnosed [1,2]. Tuberculosis PJI may result from the hematogenous spread of an extra-articular focus of active tuberculosis, or from the local reactivation of latent tuberculosis, even in patients without previously known history of tuberculosis [3]. *M. tuberculosis* PJI may also arise from an active tuberculosis of the native joint, mimicking osteoarthritis, undiagnosed by the time of arthroplasty [4]. Given the limited number of cases reported to date, the optimal strategy for the management of *M. tuberculosis* PJI is still controversial, as clinical practice guidelines for tuberculosis [5], and for PJI [6], provide no specific recommendation for *M. tuberculosis* PJI. In particular, whether the prosthetic joint needs to be removed is unclear. This question is of importance since *M. tuberculosis* PJI frequently occur in elderly patients with poor general condition and high surgical risk [3,7]. To better characterize *M. tuberculosis* PJI, we report our own experience of 13 consecutive cases, and performed a literature review, with a focus on management and outcome.

Methods

We performed a retrospective study of all patients with documented *M. tuberculosis* PJI managed from 1997 to 2016 in seven referral hospitals, members of a clinical research network, the *Groupe d'Epidémiologie et Recherche en Infectiologie Clinique Centre-Ouest* (GERICCO), in Western France. During the study period, all patients diagnosed with a *M. tuberculosis* PJI in these centers were managed by a multidisciplinary team including specialists in infectious diseases, orthopedic surgery, and microbiology. We only enrolled

patients with at least one PJI sample (i.e. joint aspirates or synovial tissue) positive for *M. tuberculosis* by culture or PCR. Patients who were previously diagnosed with native joint tuberculosis by the time of arthroplasty were not enrolled. Cases were identified through computerized databases from the microbiology departments and the infectious diseases units of the participating sites. Clinical, biological, and microbiological data were extracted from medical charts through a standardized questionnaire, as well as the type and dates of PJI surgery(ies), antituberculosis drugs, and outcome. Physicians in charge were requested to categorize the outcome as favorable, unknown, or not favorable. The study was approved by the Rennes University Hospital Institutional Review Board. For the literature review, we searched Medline and Embase for articles in English or French published before January 2018, using the keywords "prosthetic joint infection" and "tuberculosis".

Results

Between 1997 and 2016, 13 patients (8 males, 5 females, median age 79 years [range, 60-86]) were diagnosed with *M. tuberculosis* PJI in the seven participating centers. Patients characteristics are presented in Table 1. Six patients (46%) had been previously diagnosed with active tuberculosis, pulmonary (n=5), or disseminated (n=1), 2 to 56 years before the diagnosis of *M. tuberculosis* PJI. Major comorbidities were colon cancer (n=2), diabetes (n=1), and rheumatoid arthritis (n=1). PJI involved hip (n=6), knee (n=6), or shoulder (n=1). Median duration from arthroplasty to PJI diagnosis was 9 years [range, 0.4-20]. Main symptoms were pain (n=9), fever (n=6), local inflammation (n=6), and weight loss (n=6). Median white blood cells count was 6.3 G/L [range, 2.3-8.8], median CRP level was 80 mg/L [range, 14-183]). The diagnosis of *M. tuberculosis* PJI was obtained on joint aspirates (n=9), or synovial tissue (n=4). Acid-fast bacilli were observed on microscopic examination in 6 cases, and culture was positive for *M. tuberculosis* in 11 cases. In 4 patients, tuberculosis was

also documented by respiratory samples. Four patients (31%) had another active localization of tuberculosis by the time of *M. tuberculosis* PJI, including pulmonary (n=2), hepatic (n=2), pericardial, splenic, and pleural (one patient each). Nine cases were multi-susceptible tuberculosis, and two were resistant to isoniazid. Drug susceptibility testing could not be performed in two cases who were only documented through PCR. Of note, PCR was positive in all cases tested (5/5).

Treatment included antituberculosis drugs for 12 patients (median duration, 14 months [range, 6-32]), and surgery for nine patients: debridement (n=4), definitive resection arthroplasty (n=3), and revision arthroplasty (1-stage exchange, n=2). PJI could be controlled in 12 patients. Three patients died (23%), including one death attributable to tuberculosis, in a 71-year old man who died with fever, cachexia, and untreated *M. tuberculosis* PJI, as the diagnosis of tuberculosis was obtained post-mortem. The median duration of follow-up for the 10 patients who survived was 21 months after *M. tuberculosis* PJI diagnosis, and 7 months after tuberculosis treatment discontinuation [range, 0-8].

The literature review identified 70 additional observations of *M. tuberculosis* PJI (Table 2) [2,4,8-54]

They were 39 females and 31 males, with a median age of 68 years [range, 27-92]. History of previous tuberculosis was reported in 33% of cases. PJI occurred in hip (n=38), knee (n=30), shoulder (n=1), or wrist (n=1), with a median duration of one year (range, 0-38 years) between arthroplasty, and *M. tuberculosis* PJI diagnosis. Fourteen patients (20%) had at least one other site of active tuberculosis by the time of *M. tuberculosis* PJI diagnosis, including pulmonary (n=9), urinary (n=2), and adrenal gland, elbow arthritis, vertebral osteomyelitis, neuro-meningeal, disseminated tuberculosis (one patient each). Tuberculosis was mostly documented by synovial tissue histology (n=31), synovial tissue culture (n=26), joint aspirate culture (n=19), or sputum culture (n=8). Microscopic examination had a low

yield, either in synovial tissue (n=5), or in joint aspirates (n=2). Drug susceptibility testing was available for only 17 isolates, including 13 multi-susceptible, two streptomycin-resistant, one isoniazid-resistant, and one multidrug-resistant. Treatment included antituberculosis drugs for a median duration of 12 months [range, 5-36]. The outcome was reported as favorable in 11/14 patients (79%) who had no surgery, 11/13 patients (85%) who underwent debridement with prosthesis retention, 19/22 patients (86%) who had prosthesis revision (one- or two-stage exchange), and 17/21 patients (81%) who had prosthesis resection with no reimplantation (NS).

Discussion

The main findings of this case series and the literature review on *M. tuberculosis* PJI are the following: i) *M. tuberculosis* PJI occurred mostly in elderly patients, with similar numbers in males and females; ii) median time from arthroplasty to *M. tuberculosis* PJI diagnosis was one year in our case series as well as in the literature, with a large variability (from <1 month, to 38 years); iii) past medical history of active tuberculosis was found in only 33-45% of cases; iv) by the time of *M. tuberculosis* PJI diagnosis, 20-33% of patients had at least one other localization of active tuberculosis, predominantly the lungs; v) the diagnosis of *M. tuberculosis* PJI was usually obtained on synovial tissue and/or joint aspirates; vi) surgery was not a major prognostic factor, with similar rates of favorable outcome in patients who underwent resection arthroplasty, revision arthroplasty, debridement with prosthesis retention, and even in patients who had no surgery.

The latter was quite unexpected, given that surgery is an essential component of the management of PJI, when the usual pathogens are involved (e.g. staphylococci, streptococci, enterococci, Enterobacteriaceae, *Pseudomonas aeruginosa,* anaerobes) [6]. However, when combining our case series and literature data, the majority of patients with documented *M.*

tuberculosis PJI who received no surgery had a favorable outcome (14/15, 93%). Although these patients only represent 20% of *M. tuberculosis* PJI, this suggests that prolonged antituberculosis treatment may be curative in a substantial proportion of cases. The second discrepancy with the paradigms for the management of PJI is the high rate of success in patients with late PJI in whom prosthesis was retained. Indeed, this situation is usually considered as a strong indication for revision arthroplasty, either one- or two-stage. However, in six cases of our series and 12 cases in the literature [2,9,22,25,34,41,42,46,49], *M. tuberculosis* PJI developed between 12 months and 11 years after arthroplasty, but could still be controlled without removal of the prosthesis, with a management strategy including prolonged antituberculosis treatment, with or without debridement. For patients who underwent revision arthroplasty, although no definitive conclusion can be drawn from such a retrospective observational study, it must be outlined that one-stage revision arthroplasty was successful in 12/12 cases (two cases of our series, and 10 cases in the literature [25,28-30,32,34,51,52,54]).

These data suggest that basic rules for the management of *M. tuberculosis* PJI may differ from those usually applied for PJI due to other pathogens, with less emphasis on the timing of, and on the requirement for, surgical treatment. This may be of importance for the population of patients with *M. tuberculosis* PJI, mostly elderlies (median age, 79 years in our series), with comorbidities: when surgical treatment carries a high risk of severe complications or is declined by the multidisciplinary team and/or the patient himself, our study suggests that the outcome may still be favorable with prolonged antituberculosis treatment. This lower importance of surgery in the management of *M. tuberculosis* PJI may be related to the peculiar biology of *M. tuberculosis*, characterized by a much longer doubling time as compared to usual pathogens (e.g., 20-40 minutes for *Staphylococcus aureus*, and 20 hours for *M. tuberculosis*). In addition, although *M. tuberculosis* may produce biofilms [55],

two *in vitro* studies on spinal implants found that the capacity of *M. tuberculosis* for adherence and biofilm formation is dramatically reduced as compared to the usual suspects for PJI, *S. aureus*, and *S. epidermidis* [56,57]. Prolonged antituberculosis regimen including rifampicin, one of the most active antibacterials in biofilm, for a median duration of 14 months in our series and 12 months in the literature, may be curative even in the absence of surgery, for *M. tuberculosis* PJI. This doesn't imply that surgery is of no interest in the management of *M. tuberculosis* PJI, given that we could not reliably evaluate the functional outcome, due to the heterogeneity of follow-up. Surgery is most likely beneficial in specific situations such as prosthetic joint loosening (requiring exchange arthroplasty), or voluminous collection (requiring debridement and drainage). In addition, our study was not powered to analyze whether surgery could reduce the risk of late relapses.

This study has limitations. Firstly, due to its multicenter retrospective design over a long period of time (20 years), our case series has multiple potential biases: data collection and follow-up were not standardized, and the management probably differed not only from one center to another, but also over time. However, the participating centers were involved in active collaboration within the GERICCO network during the study period, and patients were managed in line with French guidelines for complex osteo-articular infections and for tuberculosis, so that differences in patient management were limited. Secondly, although this case series is larger than any other case series of *M. tuberculosis* PJI published to date, sample size remains limited. Thirdly, literature review is subject to publication bias, as successful cases are more likely to be submitted for publication and accepted, as compared to failures. Finally, as the follow-up was not standardized, the data available only allows to categorize the outcome as favorable, unknown, or not favorable. Due to the heterogeneous outcome assessment in our case series and in the literature, and the propensity of *M. tuberculosis* to remain latent over decades, we are unable to differentiate patients in whom tuberculosis was

cured, or only controlled. However, our case series included all cases of *M. tuberculosis* PJI documented within the GERICCO network during the study period, and may be considered as representative of *M. tuberculosis* PJI characteristics, management, and outcome in our area.

In conclusion, this case series and literature review suggest that the paradigms for management of *M. tuberculosis* PJI may differ from that of PJI related to other pathogens: The outcome may be favorable in most cases with prolonged antituberculosis treatment, including for patients in whom surgery could not be performed.

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Conflicts of Interest: None.

Authorship: All authors had access to the data and participated in preparation of the manuscript.

Table 1 Characteristics of patients diagnosed with *Mycobacterium tuberculosis* prosthetic joint infection (PJI) at our institutions

	Sex, age (years)	**Prior active tuberculosis (TB)**	**Prosthetic joint infected**	**Time from arthroplasty to infection**	**Documentation of *M. tuberculosis* PJI**	**Other localizations**	**Anti-TB drugs (duration, months)**	**Surgical treatment**	**Outcome (post-treatment follow-up)**
Patient 1	M, 79	Pulmonary TB during childhood	Knee	7 years	Joint aspirate (Ziehl-Neelsen, and culture)	Lung, pericardium, liver	INH/RMP (12), EMB (4), PZA (2)	No surgery	Good (1 year)
Patient 2	M, 60	Possible pulmonary TB during childhood	Hip	5 years	Joint aspirate (Ziehl-Neelsen, and culture)	-	INH/RMP (18), EMB (14)	No surgery	Good (2 years)
Patient 3	M, 84	Pulmonary TB 35 years before	Knee	11 years	Synovial tissue (PCR, and culture)	Liver, spleen	INH/RMP (9), EMB (2)	Debridement	Signs of infection resolved, sudden death
Patient 4	M, 79	Pulmonary TB 3 years before	Hip	4 years	Joint aspirate (PCR, and culture)	-	RMP/PZA (15), EMB (3), INH (1)*	Revision arthroplasty	Signs of infection resolved, Died of poor general condition
Patient 5	M, 86	No	Knee	9 years	Joint aspirate (PCR)	-	INH/RMP/OFX (6), EMB (4)	Resection arthroplasty	Good (3 months)
Patient 6	F, 85	No	Knee	14 years	Joint aspirate (Ziehl-Neelsen, and culture)	-	INH/RMP (12), EMB (2), PZA (1)	Resection arthroplasty	Good (2 months)
Patient 7	F, 82	No	Knee	9 years	Synovial tissue (Ziehl-Neelsen, and	-	INH/RMP (15), PZA (0.5)	Resection arthroplasty	Good (6 months)

					culture)				
Patient 8	M, 71	Pleural TB 1 year before	Hip	20 years	Joint aspirate (Ziehl-Neelsen, and culture)	Pleura	Untreated	Untreated	Died before diagnosis
Patient 9	F, 64	No	Shoulder	5 months	Joint aspirate (Ziehl-Neelsen, PCR, and culture)	-	INH/RMP (32), PZA (2)	Debridement	Good (3 months)
Patient 10	F, 81	No	Hip	4 years	Joint aspirate (culture)	Lungs	INH/RMP (17), EMB/PZA (2)	Debridement	Good (1 year)
Patient 11	M, 61	No	Hip	2 years	Synovial tissue (culture)	-	INH/RMP (9), EMB (3)	Debridement	Good (8 year)
Patient 12	M, 69	Disseminated TB 2 years before	Hip	10 years	Synovial tissue (PCR)	-	INH/RMP (24), EMB/PZA (6)	Revision arthroplasty	Good (6 months)
Patient 13	F, 84	No	Knee	3 years	Joint aspirate (culture)	-	INH/RMP (12), EMB/PZA (2)	No surgery	Good (still on treatment)

EMB, ethambutol; F, female; INH, isoniazid; M, male; OFX, ofloxacin; PCR, polymerase chain reaction; PZA, pyrazinamide; RMP, rifampicin; TB, tuberculosis.

* For this patient, *M. tuberculosis* isolate had primary high-level resistance to INH on drug susceptibility testing

Table 2 Cases of *Mycobacterium tuberculosis* prosthetic joint infection reported in the literature

Author, year	**Sex, age (years)**	**Prior active TB**	**Prosthetic joint infected**	**Time from arthroplasty to infection**	**Documentation of *M. tuberculosis* PJI**	**Other localizations**	**Anti-TB drugs (duration, months)**	**Surgical treatment**	**Outcome (post-treatment follow-up)**

McLaughlin, 1977 [8]	M, -	No	Hip	< 1 month	NS	-	NS (NS)	No surgery	NS
McCullough, 1977 [9]	F, 77	Possible lymph nodes TB	Hip	7 years	Synovial tissue (culture)	-	INH/RMP (18), SM (2)	Debridement	Good (6 months)
Wolfgang, 1978 [10]	F, 70	No	Hip	4 months	Synovial tissue (histology, culture)	-	NS (NS)	No surgery	NS
Mouterde, 1978 [11]	M, 37	No	Hip	12 months	NS	-	NS (NS)	Resection arthroplasty	NS
Besser, 1980 [12]	M, 65	No	Knee	< 1 month	Synovial tissue (histology)	-	NS (12)	No surgery	Good (1 year)
Carbon, 1981 [13]	F, 40	No	Hip	8 months	NS	-	NS (NS)	Resection arthroplasty	Good (5 years)
Carbon, 1981 [13]	M, 74	No	Hip	2,5 years	NS	-	NS (NS)	Resection arthroplasty	Good (5 years)
Olsson, 1981 [14]	M, 64	No	Hip	2 years	NS	-	NS (NS)	Revision arthroplasty (partial)	NS
Bryan, 1982	F, 72	No	Knee	8 years	Joint aspirate	Elbow arthritis	INH/RMP/PZA	Arthrodesis	Good (3 years)

[15]					(culture)		(24)		
Hecht, 1983 [16]	M, 27	Possible hip TB	Hip	3 months	Joint aspirate (culture)	-	INH/EMB (NS)	Resection arthroplasty	Good (1 year)
Zeiger, 1984 [17]	F, 40	NA	Knee	4 years	Synovial tissue (culture)	-	NS (NS)	Resection arthroplasty	NS
Levin, 1985 [18]	F, 81	No	Hip	4 years	NS	-	INH/RMP (36), SM (3.5)	Resection arthroplasty	Good (2.5 months)
Wolfgang, 1985 [19]	M, 61	No	Knee	13 months	Joint aspirate (culture)	-	INH/RMP (24)	Staged exchange	Good (1 year)
Delrieu, 1986 [20]	F, 69	No	Hip	12 months	NS	-	NS (NS)	Resection arthroplasty	Good (2 years)
Delrieu, 1986 [20]	F, 75	No	Hip	10 years	NS	-	NS (NS)	Resection arthroplasty	Good (3 years)
Lin, 1986 [21]	F, 70	No	Hip	8 months	NS	-	NS (NS)	No surgery	Good (4 years)
Lin, 1986 [21]	F, 49	No	Hip	8 months	Synovial tissue (histology)	-	NS (NS)	No surgery	Good (3 years)
Wray, 1987 [4]	M, 62	No	Knee	< 1 month	Synovial tissue (histology, culture)	Lungs	INH/RMP/EMB (12)	No surgery	Good (5 years)

Wray, 1987 [4]	M, 63	No	Knee	< 1 month	Synovial tissue (histology) + Sputum (culture)	Lungs	INH/RMP (12)	No surgery	Good (1.5 years)
Eskola, 1988 [22]	M, 47	Possible knee TB	Knee	18 months	Joint aspirate (culture)	-	INH/RMP/EMB (12)	Debridement	Good (2 years)
Baldini,1988 [23]	M, 61	No	Hip	2 years	Synovial tissue (culture)	-	NS (NS)	Resection arthroplasty	Good (4 months)
Gale, 1991 [24]	M, 67	No	Knee	< 1 month	Synovial tissue (histology) + Sputum (culture)	Lungs	INH/RMP (12), EMB (6)	No surgery	Good (10 years)
Callaghan and Vail, 1994 [25]	M, 79	No	Knee	10 years	NS	-	NS (NS)	Revision arthroplasty	NS
Lusk, 1995 [26]	F, 75	No	Knee	15 years	Synovial tissue (histology, culture)	-	INH/PZA (6), RMP (1), EMB (5)	Resection arthroplasty	Died (6 months)
Tokumoto, 1995 [27]	F, 72	No	Hip	3 years	Synovial tissue (culture)	-	INH/RMP (12)	Resection arthroplasty	NS
Tokumoto, 1995 [27]	F, 71	Hip TB	Knee	20 months	Joint aspirate (culture)	-	INH/EMB (18)	Resection arthroplasty	Good (8 years)

Tokumoto, 1995 [27]	F, 70	No	Knee	38 years	Joint aspirate (culture)	-	INH/RMP (12)	Resection arthroplasty	Good (2 years)
Ueng, 1995 [28]	M, 40	No	Hip	15 years	Joint aspirate (culture)	Lungs	INH/RMP/EMB (12)	Resection arthroplasty	Good (>1 year)
Ueng, 1995 [28]	M, 62	No	Hip	18 months	Synovial tissue (culture)	Lungs	INH/RMP/PZA (24)	Revision arthroplasty	Good (3 years)
Kreder, 1996 [29]	F, 66	No	Hip	4 years	NS	-	INH/EMB/PZA (9), RMP (NS)	Revision arthroplasty (partial)	Good (18 months)
Spinner, 1996 [25]	F, 70	No	Knee	4.5 years	Synovial tissue (culture)	-	INH (NS), RMP/EMB (12)	Debridement	Good (2.5 years)
Carlsson, 1997 [30]	M, 75	Knee TB	Hip	4 months	Synovial tissue (histology, culture, PCR)	-	INH/RMP (12), PZA (2)	Revision arthroplasty	Good (6 months)
Berbari, 1998 [31]	F, 44	No	Hip	23 years	NS	-	INH/EMB (16)	Resection arthroplasty	Good (8 years)
Berbari, 1998 [31]	M, 60	No	Hip	30 years	NS	-	INH/EMB (19), RMP (1)	Resection arthroplasty	Good (10 years)
Berbari,	F, 52	No	Hip	10 years	NS	-	INH/RMP (15)	Staged exchange	Good (7 years)

1998 [31]									
Krappel, 2000 [32]	F, 67	Peritoneal & pleural TB	Hip	2 months	Synovial tissue (histology)	-	INH/RMP (12), SM (3), PZA (NS)	Revision arthroplasty (partial)	Good (2.5 years)
Hugate, 2002 [33]	M, 71	Knee TB	Hip	5 months	Synovial tissue (culture)	-	INH/RMP/EMB (12), PZA (NS)	Debridement	Good (1.2 years)
Boeri, 2003 [34]	F, 55	No	Hip	2 years	Joint aspirate (culture)	-	INH/RMP (17), EMB/PZA (4)	No surgery	Good (9 months)
Boeri, 2003 [34]	F, 47	Possible hip TB	Hip	3 years	Synovial tissue (culture)	-	INH/RMP (6), EMB/PZA (3)	Revision arthroplasty	Good (8 years)
Fernandez-Valencia, 2003 [35]	M, 78	No	Hip	6 months	Synovial tissue (histology)	-	INH/RMP (9), EMB (3)	Resection arthroplasty	Good (6 years)
Al Shaikh, 2003 [36]	F, 73	No	Knee	8 months	Synovial tissue (culture)	-	INH/RMP/PZA (12), EMB (9)	Debridement, delayed arthrodesis	Good (1 year)
Marmor, 2004 [37]	M, 66	No	Knee	2 months	Joint aspirate, blood (culture)	Disseminated	INH/RMP/PZA (6)	2-stage revision arthroplasty	Good (5 years)
Marmor, 2004 [37]	F, 65	Possible hip TB	Knee	3 months	Joint aspirate (culture)	Urinary tract	INH/RMP/PZA (6)	2-stage revision arthroplasty	Good (7 years)

Marmor, 2004 [37]	F, 77	No	Knee	4 months	Joint aspirate (culture)	-	INH/EMB/PZA (8)	Debridement	Good (1.5 years)
Kaya et al, 2006 [38]	F, 72	No	Hip	9 years	Synovial tissue (culture)	Lungs	INH/EMB/PZA (NS)	Resection arthroplasty	Good (6 months)
Kadakia, 2007 [39]	F, 85	No	Knee	< 1 month	Joint aspirate (Ziehl-Neelsen)	Lungs	NS (6)	No surgery	Good (NS)
Khater, 2007 [40]	F, 75	No	Knee	3 months	Synovial tissue (histology, culture)	-	INH/EMB (18), RMP (NS)	Resection arthroplasty	Good (18 months)
Shanbhag, 2007 [41]	F, 59	No	Hip	15 months	Joint aspirate (culture)	-	RMP/EMB/PZA (12)	Debridement	Good (1.5 years)
Wang, 2007 [42]	M, 72	Pulmonary TB	Knee	3 years	Synovial tissue (culture)	Lungs	INH/RMP/EMB/PZA (0.7)	Debridement	Died (1 month)
De Haan, 2008 [43]	F, 75	Knee TB	Knee	3 months	Synovial tissue (culture)	-	INH/RMP/EMB/PZA (9)	Debridement	Good (NS)
Marschall, 2008 m[44]	M, 48	No	Knee	9 months	Joint aspirate (culture)	Lungs, Neuro-meningeal	INH/EMB/PZA (1), MOX (0.5), RMP (0.5)	No surgery	Died (1 month)
Lee, 2009 [45]	F, 79	No	Knee	2 months	Synovial tissue (histology)	-	INH/RMP/EMB/PZA (12)	Debridement	Good (13 months)

Neogi, 2009 [46]	F, 73	No	Knee	14 years	Synovial tissue (PCR)	-	INH/RMP (18), EMB (4), PZA (7)	No surgery	Good (3 years)
Upton, 2009 [47]	M, 39	CNS, urinary, joint TB	Hip	4 years	Joint aspirate (culture)	Vertebral osteomyelitis, Urinary tract	MOX/RMP (31), AMK/CS (2), PZA (4)	2-stage revision arthroplasty	Good (1.7 years)
Mete, 2012 [48]	F, 32	No	Hip	5 years	Synovial tissue (culture)	-	INH/RMP (12), EMB/PZA (2)	2-stage revision arthroplasty	Good (1 year)
De Nardo, 2012 [49]	F, 67	Possible pulmonary TB	Hip	16 months	Joint aspirate (PCR)	Adrenal glands	INH/RMP (>18), EMB/PZA (3)	Debridement	Good (1 year)
Klein, 2012 [50]	F, 36	Genital TB	Knee	11 months	Synovial tissue (culture)	-	INH/RMP/EMB/PZA/MOX (19)	2-stage revision arthroplasty	Good (3 years)
Carrega, 2013 [51]	F, 92	No	Hip	3 years	Synovial tissue (culture)	-	INH/EMB (9), RMP (1), LVX (NS)	Revision arthroplasty	Good (6 months)
Carrega, 2013 [51]	M, 68	No	Wrist	2 years	Synovial tissue (culture)	-	INH/RMP (14), EMB/PZA (2)	Revision arthroplasty	Infection cured, but functional impairment (NS)
Carrega,	F, 79	No	Hip	< 1 month	Synovial tissue	-	INH/RMP/EMB (5)	2-stage revision	Good (1 year)

2013 [51]					(culture)			arthroplasty	
Carrega, 2013 [51]	F, 72	No	Hip	7 years	Synovial tissue (culture)	-	INH/RMP (12), PZA (2)	2-stage revision arthroplasty	Good (1 year)
Carrega, 2013 [51]	F, 80	No	Knee	< 1 month	Synovial tissue (histology, culture)	-	INH/RMP (14), PZA (2)	2-stage revision arthroplasty	Good for TB, but died of heart attack (6 months)
Harwin, 2013 [52]	F, 60	No	Knee	7 months	Synovial tissue (culture)	-	INH/RMP (21), EMB/PZA (12)	Revision arthroplasty	Good (2 years)
Tekin Koruk, 2013 [53]	M, 55	No	Knee	20 days	Joint aspirate (culture)	-	INH/RMP (12), EMB/PZA (2)	No surgery	Good (18 months)
Seng, 2016 [2]	5 cases	Yes (3/5)	Hip (4/5) Knee (1/5)	34 months (mean)	NS	-	NS (mean 11)	No surgery (1/5) Debridement (1/5) 2-stage revision arthroplasty (3/5)	Good: 4/5 (mean, 24 months); one patient died of disseminated TB
von Keudell, 2016 [54]	M, 84	Pulmonary TB	Knee	5 months	NS	-	INH/RMP (>15), EBB/PZA (12)	Revision arthroplasty (partial)	Good (1.3 years)

AMK, amikacin; CNS, central nervous system; CS, cycloserine; d, days; EMB, ethambutol; F, female; INH, isoniazid; LVX, levofloxacin; M, male; mo, month(s); MOX, moxifloxacin; NS, not specified; OFX, ofloxacin; PCR, polymerase chain reaction; PZA, pyrazinamide; RMP, rifampicin; SM, streptomycin; TB, tuberculosis; y, year(s)

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