J. Bone Joint Infect., 8, 11–17, 2023
https://doi.org/10.5194/jbji-8-11-2023

JBJI Journal of Bone and Joint Infection Open Access

Clinical–epidemiological profile of confirmed cases of osteoarticular tuberculosis

Caroline Thomaz Panico, Priscila Rosalba Domingos de Oliveira, Vladimir Cordeiro de Carvalho, Angélica Makio dos Anjos, Vanessa Ferreira Amorim de Melo, and Ana Lucia Lei Munhoz Lima

Instituto de Ortopedia e Traumatologia, Faculdade de Medicina FMUSP,
Universidade de São Paulo, São Paulo, Brazil

Correspondence: Priscila Rosalba Domingos de Oliveira (priscila.rosalba@hc.fm.usp.br)

Received: 13 June 2022 – Revised: 25 November 2022 – Accepted: 7 December 2022 – Published: 5 January 2023

Abstract. **Introduction**: tuberculosis (TB) remains a major cause of morbidity and mortality worldwide. The incidence of TB has increased since the 1980s. Given the increasing prevalence of TB worldwide, osteoarticular TB (OATB) is a significant health problem. **Methods**: retrospective study of a case series of hospitalized patients with confirmed OATB by culture or histopathological examination who were seen at a reference orthopedic hospital in São Paulo, Brazil, from 2014 to 2019. **Results**: thirty patients with confirmed bone and joint TB were seen from 2014 to 2019. The main sites of OATB were the spine (83.3 %) and the appendicular skeleton (26.7 %). Indication of surgical treatment was significantly related to the need for hospitalization ($p = 0.009$) and the increased length of hospital stay ($p = 0.005$). Presence of sequelae at the end of treatment was correlated with the presence of motor deficit at the time of OATB diagnosis ($p = 0.035$) as well as with initial presence of functional limitation ($p = 0.025$) and with high value of C-reactive protein at the end of treatment ($p = 0.037$). **Conclusions**: the delay in the onset of clinical and laboratory signs of cases of osteoarticular infections hinders the early diagnosis and treatment of the disease, resulting in major complications sometimes requiring surgical treatment and consequently leading to a prolonged hospital stay, evidence of high inflammatory activities, and the presence of neurological deficits.

1 Introduction

Tuberculosis (TB) is an important public health problem, with serious medical, social, and financial impacts, especially in developing countries. The main etiological agent of this disease is the bacterium *Mycobacterium tuberculosis*. Every year, approximately 3 million people with TB remain undiagnosed and continue to spread the disease in the community, making it difficult to control. When TB occurs in organ systems other than the lungs, it is called extrapulmonary TB (EPTB). Musculoskeletal TB is responsible for 10–15 % of all EPTB cases. Spinal TB is the most common form of skeletal TB, accounting for approximately 50 % of all cases (Malaviya, 2003).

2 Materials and methods

A retrospective study was conducted on a series of patients with a diagnosis of OATB confirmed by culture or histological examination seen at the Instituto de Ortopedia e Traumatologia do Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo from 2014 to 2019. For the analysis of outcomes, remission was defined as the absence of signs and symptoms of infection activity 6 months after the end of treatment. The permanence of motor or sensory sequelae related to the initial onset of OATB was analyzed separately.

Quantitative variables were described using summary measures (mean and standard deviation or median) and compared between groups using Student's t-tests or Mann–Whitney tests. Qualitative variables were described using absolute and relative frequencies. The existence of association between variables was verified with chi-square tests or exact

Table 1. Clinical and demographic characteristics of 30 patients with OATB seen between 2014 and 2019.

Variable		
Sex	$N = 30$	N (%)
Male	16	53.3
Female	14	46.6
Ethnicity	$N = 30$	N (%)
White	15	50.0
Other	8	26.6
Black	6	20.0
Ignored	1	3.3
Age (years)		
Mean ± SD	41.7 ± 17.3	
Median (min; max)	40 (2; 79)	
Initial treatment regimen	$N = 30$	N (%)
Inpatient	22	73.3
Outpatient	8	26.6
Mean number of days hospitalized ($N = 22$) ± SD	36.5 ± 34.3	
Comorbidities	$N = 30$	N (%)
Presence of comorbidities	22	73.3
Types of comorbidities	$N = 22$	N (%)
Cardiometabolic diseases	7	31.8
Rheumatic diseases	2	9.1
Neoplasm	2	9.1
Mental disorder	1	4.5
Substance abuse	6	27.3
Other	4	18.2
HIV serology status known	$N = 30$	N (%)
HIV positive	1	3.3
OATB type	$N = 30$	N (%)
Disseminated TB	12	40.0
Spinal TB	25	83.3
TB in appendicular skeleton	8	26.7
Spinal level affected	$N = 25$	N (%)
Thoracic	9	36.0
Thoraco-lumbar	7	28.0
Lumbar	6	24.0
Lumbosacral	2	8.0
Thoracic, lumbar, and sacral	1	4.0
Appendicular site	$N = 8$	N (%)
Knee	4	50.0
Hip	1	12.5
Tibia	1	12.5
Ankle	1	12.5
Forearm	1	12.5
Culture for mycobacteria performed on bone tissue	$N = 30$	N (%)
Culture positive	23	76.6

Table 1. Continued.

Variable		
Histopathological examination performed on bone tissue	$N = 30$	N (%)
Suggestive of TB	21	70.0
Not suggestive	8	26.6
Result not available	1	3.3
Ziehl Nielson stain (ZNS) test performed	$N = 30$	N (%)
ZNS positive	3	10.0
Pulmonary radiological examination performed	$N = 23$	N (%)
Finding compatible with pulmonary TB	10	43.5
C-reactive protein (CRP) measured at the beginning of treatment	$N = 30$	N (%)
Elevated	28	93.3
CRP levels at beginning of treatment ($mg\,L^{-1}$)		
Mean ± SD	66.5 ± 65.4	
Median (min; max)	45.1 (1.3; 309.6)	
CRP levels at end of treatment ($mg\,L^{-1}$)		
Mean ± SD	10.3 ± 13.2	
Median (min; max)	3.8 (0.7; 42.9)	

Table 2. Signs and/or symptoms described for the 30 patients with OATB (*).

Signs and/or symptoms	$N = 30$	N (%)
Functional limitation	24	80.0
Back pain	22	73.3
Motor deficit	17	56.6
Limb pain	11	36.6
Paresthesia	10	33.3
Weight loss	9	30.0
Limb edema	7	23.3
Fever	6	20.0
Sinus tract	4	13.3
Deformity	3	10.0
Cough	3	10.0
Chills	2	6.7

Table 3. Type of neurological deficit present.

Type of deficit	$N = 17$	N (%)
Paraparesis	9	52.9
Paraplegia	6	35.3
Tetraparesis	1	5.8
Unilateral paresis	1	5.8

tests (Fisher's exact test or likelihood ratio test). IBM-SPSS for Windows version 20.0 software was used to do the analyses. Data were tabulated using Microsoft Excel 2003 software. The tests were performed at a significance level of 5 %. (Kirkwood and Sterne, 2006).

3 Results

In this survey, 30 patients with confirmed OATB were found from 2014 to 2019 at our hospital. Among them, 73.3 % required hospitalization, mainly for diagnostic investigation, with a case fatality rate of 3.3 % and an average length of stay of 36.5 d. Of the patients, 46.6 % had TB in more than one organ and 40 % had pulmonary TB concomitantly. Main sites of OATB were spine (83.3 %), with greater involvement of the thoracic spine (36 %). Among the 30 patients, 26.7 % had TB in the appendicular skeleton, with knee involvement in 50 %. Diagnosis was confirmed by *M. tuberculosis* complex isolation in culture in 76.6 % of patients. Only 10 % had a positive screening for acid-fast bacilli (AFB) by conventional sputum smear microscopy test. In the investigation of disseminated TB, 20 patients underwent chest X-ray and 43.4 % of those had signs suggestive of pulmonary TB. Regarding laboratory tests, 93.3 % had altered C-reactive protein levels, with a mean of 68.4 (normal reference value $<5.0\,mg\,mL^{-1}$). The mean value of this test at the end of treatment was 10.3. Table 1 describes the main clinical and demographic variables of patients.

Table 4. Type of treatment for the 30 patients with OATB.

Treatment	$N = 30$	N (%)
Antituberculosis drugs only	30	100
Antituberculosis drugs and surgery	17	56.6
Type of surgical treatment	$N = 17$	N (%)
Debridement and spinal arthrodesis	11	64.7
Debridement	6	35.3
Antituberculous drugs used		
Phase 1 medication	$N = 30$	N (%)
RIPE[1]	24	80
RIP[2]	2	6.7
RIE[3]	3	10
IPE[4]	1	3.3
Other phase 1 medications	$N = 2$	N (%)
Streptomycin	1	50
Levofloxacin and streptomycin	1	50
Phase 2 medication	$N = 30$	N (%)
Rifampicin and isoniazid	27	90
Isoniazid	1	3.3
Other	2	6.6
Other phase 2 medications	$N = 2$	N (%)
Levofloxacin and ethambutol	1	50
Pyrazinamide + streptomycin	1	50
Mean treatment time (days)	316.9	

RIPE[1]: rifampicin, isoniazid, pyrazinamide, and ethambutol. RIP[2]: rifampicin, isoniazid, and pyrazinamide. RIE[3]: rifampicin, isoniazid, and ethambutol. IPE[4]: isoniazid, pyrazinamide, and ethambutol.

Table 5. Outcomes after 6 months of follow-up for the 30 patients included in the study.

Outcome at 6 months	$N = 30$	N (%)
Remission	22	73.3
Death	1	3.3
Recurrence	0	0.0
Lost to follow-up	2	6.7
Has not yet completed follow-up time at the time of analysis	5	16.7

The mean interval between the onset of symptoms to diagnosis was 358 d. Table 2 demonstrates the main signs and symptoms described for the 30 patients. 17 patients had some type of neurological deficit associated with the diagnosis of OATB, as described in Table 3.

All patients received antituberculous treatment as recommended by the Brazilian Guidelines (Ministério da Saúde, 2022) and 56.6 % of patients also underwent surgical treatment. Regarding the surgical treatment used, debridement and spine arthrodesis was performed in 64.71 % of the patients and debridement was performed in 35.2 % of the patients (Table 4).

Table 6. Type of sequelae present at the end of the follow-up period.

Sequel type	$N = 18$	N (%)
Pain	7	38.9
Paresthesia	1	5.5
Paraplegia	4	22.2
Paresis	2	11.1
Other	4	22.2

Most patients (73.3 %) achieved remission after the 6-month follow-up period and only one patient died due to cardiac complications after surgical procedures, as shown in Table 5. Among the patients who went into remission however, 18 patients (60 %) had some type of sequelae, with chronic pain being described in 61 % of patients, followed by paraplegia (22 %), paresis (11 %), and paresthesia (5.5 %) (Table 6). One case had spinal deformity (kyphosis) in association with lower back pain.

When the medical variables were correlated with the need for surgical treatment, it was found that patients who required surgery had a greater need for hospitalization and a longer duration of hospital stay ($p < 0.05$) (Table 7). Median number of hospitalization days was 46 d. Median time of symptoms in the group with surgical treatment was 150 d, while in the group with clinical treatment, it was 180 d.

There was no statistically significant difference when analyzing the clinical characteristics of patients and the risk of developing sequelae at the end of treatment, although patients with comorbidities tended to have more sequelae at the end of treatment (91.7 versus 61.1, $p = 0.099$), as shown in Table 8.

In the analysis of the association between the results of diagnostic tests performed at the beginning and during the treatment and the presence of sequelae at the end of the treatment, it was found that the high value of CRP (mg L^{-1}) at the end of treatment was significantly correlated with sequelae at the end of treatment (median 1.5 versus 6.4, $p = 0.037$), as shown in Table 9.

4 Discussion

Diagnosis of OATB can be challenging. The microscopic examination (Ziehl Neelson stain or ZNS) is less useful for paucibacillary diseases. Mycobacterial culture has a high sensitivity for the diagnosis of TB (Forbes et al., 2018). In this study, the presence of *M. tuberculosis* isolated in culture was found in 76.67 % of the cases. Only 10 % had a positive ZNS test.

Table 7. Description of the need for surgical treatment according to length of hospital stay and patient symptoms and results of statistical tests.

Variable	Surgical treatment			
	No ($N = 13$)	Yes ($N = 17$)	Total ($N = 30$)	p
Hospitalization, n (%)				0.009[a]
No	7 (53.8)	1 (5.9)	8 (26.7)	
Yes	6 (46.2)	16 (94.1)	22 (73.3)	
Length of hospital stay (days)				0.005[b]
mean ± SD	20 ± 32.6	49.1 ± 30.7	36.5 ± 34.3	
median (min; max)	0 (0; 111)	46 (0; 102)	31.5 (0; 111)	

Chi-square test. [a] Fisher's exact test. [b] Mann–Whitney test.

Table 8. Patient characteristics and development of sequelae.

Variable	Sequelae		Total ($N = 30$)	p
	No ($N = 12$)	Yes ($N = 18$)		
Age (years)				0.686[c]
mean ± SD	43.3 ± 22	40.7 ± 13.9	41.7 ± 17.3	
median (min; max)	47 (2; 79)	40 (14; 66)	40 (2; 79)	
Sex, n (%)				0.765
Male	6 (50)	10 (55.6)	16 (53.3)	
Female	6 (50)	8 (44.4)	14 (46.7)	
Ethnicity, n (%)				0.241[b]
White	6 (50)	9 (50)	15 (50)	
Black	1 (8.3)	5 (27.8)	6 (20)	
Other	5 (41.7)	3 (16.7)	8 (26.7)	
Comorbidities, n (%)				0.099[a]
No	1 (8.3)	7 (38.9)	8 (26.7)	
Yes	11 (91.7)	11 (61.1)	22 (73.3)	

Chi-squared test. [a] Fisher's exact test. [b] Likelihood ratio test. [c] Student's t-test.

In the investigation of disseminated TB, 43.48 % of the patients in this study had radiological findings suggestive of pulmonary TB, in contrast to lower incidences described in literature (Hogan et al., 2019).

Back pain is the most cited symptom in the literature (Ferrer et al., 2012). In our study, 73.3 % patients had lower back pain. The mean time from symptoms to diagnosis was 358 d, suggesting a late diagnosis.

The guidelines suggest that surgery should be considered in patients with Pott's disease with significant neurological deficits and those who do not respond to medical therapy (Hogan et al., 2019; Malaviya, 2003). During the treatment of the patients in our study, 56.6 % of the patients underwent surgical procedures.

In the current study, 73.3 % of patients had remission of the condition, but, in spite of that, 60 % had some type of sequelae. This may be related to the delay in the diagnosis of tuberculosis, leading to irreversible motor or sensory deficits even with treatment of the infection. The variables that were statistically relevant when associated with the presence of sequelae were functional limitation ($p = 0.026$) and motor deficit ($p = 0.035$), as previously reported (Wang et al., 2016).

Patients requiring surgery were hospitalized for longer periods than those in the group receiving only antituberculostatic treatment (Medeiros et al., 2007; Wang et al., 2016).

In several reports, there were increased levels of CRP in the initial phase, with decreases occurring throughout treatment (Forbes et al., 2018; Mbuh et al., 2019; Muller et al., 2013). In the present study, there was a significant association between a higher value of CRP (median = 6.4 mg dL^{-1})

Table 9. Diagnostic testing and development of sequelae.

Variable	Sequelae		Total ($N = 30$)	p
	No ($N = 12$)	Yes ($N = 18$)		
Culture, n (%)				>0.999[a]
Negative	3 (25)	4 (22.2)	7 (23.3)	
Positive	9 (75)	14 (77.8)	23 (76.7)	
TB suggestive histopathological examination, n (%)				>0.999[a]
Negative	3 (25)	5 (29.4)	8 (27.6)	
Positive	9 (75)	12 (70.6)	21 (72.4)	
TB suggestive radiological findings, n (%)				0.128[a]
Negative	4 (33.3)	1 (5.6)	5 (16.7)	
Positive	8 (66.7)	17 (94.4)	25 (83.3)	
ZNS test, n (%)				>0.999[a]
Negative	11 (91.7)	16 (88.9)	27 (90)	
Positive	1 (8.3)	2 (11.1)	3 (10)	
TB suggestive pulmonary radiological findings, n (%)				>0.999[a]
Negative	3 (25)	4 (22.2)	7 (23.3)	
Positive	9 (75)	14 (77.8)	23 (76.7)	
CRP at the beginning of treatment ($mg\,L^{-1}$)				0.465[b]
mean ± SD	55.6 ± 51.6	73.8 ± 73.7	66.5 ± 65.4	
median (min; max.)	36.9 (1.3; 165.4)	57.9 (6.9; 309.6)	45.1 (1.3; 309.6)	
CRP at end of treatment ($mg\,L^{-1}$)				0.037[b]
Mean ± SD	6.2 ± 12.3	12.9 ± 13.4	10.3 ± 13.2	
Median (min; max.)	1.5 (0.7; 42.9)	6.4 (1.3; 39.4)	3.8 (0.7; 42.9)	

Chi-squared test. [a] Fisher's exact test. [b] Mann–Whitney test.

at the end of treatment and the presence of long-term sequelae ($p<0.037$).

5 Conclusion

In a reference hospital for the treatment of osteoarticular diseases, 30 patients with OATB were confirmed from 2014 to 2019. Pulmonary TB with concomitant OATB was evident in 40 % of patients. The main sites of OA infection were the spine (83.3 %) and 26.6 % had TB in the appendicular skeleton.

The need for surgical treatment was significantly correlated with the need for hospitalization ($p = 0.009$) and the increased length of hospital stay ($p = 0.005$). The presence of sequelae at the end of treatment was correlated with the presence of motor deficit at the beginning of treatment ($p = 0.035$) as well as with the initial presence of functional limitation ($p = 0.025$) and with the high value of CRP at the end of treatment ($p = 0.037$).

Data availability. Data is available under the following DOI: https://doi.org/10.17605/OSF.IO/Y4Q6R (de Oliveira, 2022).

Author contributions. CTP, PRDdO, and ALLML planned the campaign; CTP performed the measurements; CTP, PRDdO, and ALLML analyzed the data; CTP and PRDdO wrote the paper draft; and CTP, PRDdO, ALLML, VCdC, AMdA, and VFAdM reviewed and edited the paper.

Competing interests. The contact author has declared that none of the authors has any competing interests.

Ethical statement. This study was approved by the Ethics and Research Committee, CAPPesq, through the Brazil Platform. CAAE: 30921420200000068.

Disclaimer. Publisher's note: Copernicus Publications remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Acknowledgements. The authors with to thank the hospital infection control team that contributed with administrative support and data collection for this study.

Review statement. This paper was edited by Gina Suh and reviewed by three anonymous referees.

References

de Medeiros, R. S., Abdo, R. C. T., de Paula, F. C., Narazaki, D. K., dos Correia, L. S., de Araújo, M. P., Cristante, A. F., Iutaka, A. S., Marcon, R. M., Oliveira, R. P., and de Barros Filho, T. E. P.: Tratamento da tuberculose da coluna vertebral: conservador ou cirúrgico?, Acta Ortop. Bras., 15, 128–131, https://doi.org/10.1590/S1413-78522007000300001, 2007.

de Oliveira, P. R. D.: Clinical–epidemiological profile of confirmed cases of osteoarticular tuberculosis, ODF [data set], https://doi.org/10.17605/OSF.IO/Y4Q6R, 2022.

Ferrer, M. F., Torres, L. G., Ramírez, O. A., Zarzuelo, M. R., and del Prado González, N.: Tuberculosis of the spine. A systematic review of case series, Int. Orthop., 36, 221–231, https://doi.org/10.1007/s00264-011-1414-4, 2012.

Forbes, B. A., Hall, G. S., Miller, M. B., Novak, S. M., Rowlinson, M.-C., Salfinger, M., Somoskövi, A., Warshauer, D. M., and Wilson, M. L.: Practical Guidance for Clinical Microbiology Laboratories: Mycobacteria, Clin. Microbiol. Rev., 31, e00038-17, https://doi.org/10.1128/CMR.00038-17, 2018.

Hogan, J. I., Hurtado, R. M., and Nelson, S. B.: Mycobacterial Musculoskeletal Infections, Thorac. Surg. Clin., 29, 85–94, https://doi.org/10.1016/j.thorsurg.2018.09.007, 2019.

Kirkwood, B. R. and Sterne, J. A. C.: Essential Medical Statistics, 2nd edn., Blackwell Science, Massachusetts, USA, Blackwell Publishing, ISBN 0865428719, 2006.

Malaviya, A.: Arthritis associated with tuberculosis, Best Pract. Res. Clin. Rheumatol., 17, 319–343, https://doi.org/10.1016/S1521-6942(02)00126-2, 2003.

Mbuh, T. P., Ane-Anyangwe, I., Adeline, W., Thumamo Pokam, B. D., Meriki, H. D., and Mbacham, W. F.: Bacteriologically confirmed extra pulmonary tuberculosis and treatment outcome of patients consulted and treated under program conditions in the littoral region of Cameroon, BMC Pulm. Med., 19, 17, https://doi.org/10.1186/s12890-018-0770-x, 2019.

Ministério da Saúde: Manual de Recomendações para o Controle da Tuberculose no Brasil, https://www.saude.gov.br/, last access: 18 April 2022.

Muller, B. L. A., de Ramalho, D. M. P., dos Santos, P. F. G., Mesquita, E. D. D., Kritski, A. L., and Oliveira, M. M.: Inflammatory and immunogenetic markers in correlation with pulmonary tuberculosis, J. Bras. Pneumol., 39, 719–727, https://doi.org/10.1590/S1806-37132013000600011, 2013.

Wang, H., Yang, X., Shi, Y., Zhou, Y., Li, C., Chen, Y., Yu, H., Wang, Q., Liu, J., Cheng, J., Zhao, Y., Han, J., and Xiang, L.: Early predictive factors for lower-extremity motor or sensory deficits and surgical results of patients with spinal tuberculosis: A retrospective study of 329 patients, Medicine, 95, e4523, https://doi.org/10.1097/MD.0000000000004523, 2016.