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World J Orthop 2022 March 18; 13(3): 212-338



REVIEW

- 212 Conservative treatment of knee osteoarthritis: A review of the literature
Lim WB, Al-Dadah O

MINIREVIEWS

- 230 Patient-specific instrumentation in total ankle arthroplasty
Mazzotti A, Arceri A, Zielli S, Bonelli S, Viglione V, Faldini C
- 238 Diagnosis, treatment and complications of radial head and neck fractures in the pediatric patient
Macken AA, Eygendaal D, van Bergen CJ

ORIGINAL ARTICLE**Retrospective Cohort Study**

- 250 Functional and radiological outcomes of different pin configuration for displaced pediatric supracondylar humeral fracture: A retrospective cohort study
Radaideh AM, Rusan M, Obeidat O, Al-Nusair J, Albustami IS, Mohaidat ZM, Sunallah AW

Retrospective Study

- 259 Accuracy of shoulder joint injections with ultrasound guidance: Confirmed by magnetic resonance arthrography
Kuratani K, Tanaka M, Hanai H, Hayashida K
- 267 Comparative study of intertrochanteric fracture fixation using proximal femoral nail with and without distal interlocking screws
Lil NA, Makwana VR, Patel TD, Patel AR
- 278 Ilizarov bone transport combined with the Masquelet technique for bone defects of various etiologies (preliminary results)
Borzunov DY, Kolchin SN, Mokhovikov DS, Malkova TA
- 289 Diagnostic role of Xpert-MTB RIF assay in osteoarticular tuberculosis: A retrospective study
Mohanty M, Mishra B, Jain M, Karaniveed Puthiyapura L

Prospective Study

- 297 Plate *vs* reverse shoulder arthroplasty for proximal humeral fractures: The psychological health influence the choice of device?
Maccagnano G, Solarino G, Pesce V, Vicenti G, Coviello M, Nappi VS, Giannico OV, Notarnicola A, Moretti B

SYSTEMATIC REVIEWS

- 307** Impact of enhanced recovery pathways on safety and efficacy of hip and knee arthroplasty: A systematic review and meta-analysis
Heymans MJ, Kort NP, Snoeker BA, Schotanus MG
- 329** Surgical treatment of femoral deformities in polyostotic fibrous dysplasia and McCune-Albright syndrome: A literature review
Gorgolini G, Caterini A, Nicotra L, De Maio F, Efremov K, Farsetti P

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Retrospective Study

Diagnostic role of Xpert-MTB RIF assay in osteoarticular tuberculosis: A retrospective study

Monalisa Mohanty, Baijayantimala Mishra, Mantu Jain, Lubaib Karaniveed Puthiyapura

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Abstract

BACKGROUND

Osteoarticular tuberculosis (OATB) is a severe form of extrapulmonary tuberculosis (TB), which causes notable morbidity and warrants a high index of suspicion for prompt management. The diagnosis of OATB poses a challenge, because of the difficulty of collecting the samples and, secondarily, the paucibacillary nature of lesion, which gives poor sensitivity and reproducibility, with long turnaround time of routine/conventional laboratory tests and the requirement for invasive procedures and expertise. The Xpert MTB/RIF assay has been approved by the World Health Organization as a rapid diagnostic tool for diagnosing pulmonary and extrapulmonary TB.

AIM

To emphasize the diagnostic efficiency of gene Xpert for OATB in suspected patients in a tertiary care hospital of Eastern India.

METHODS

This retrospective study was conducted in the Department of Microbiology and Orthopaedics by analyzing the data of the gene Xpert assay over a 3-year duration from January 2018 to February 2021. Demographic and clinical data were recorded. The diagnostic efficiency of gene Xpert was evaluated against the composite reference standard (CRS).

RESULTS

A total of 37 cases fell into positive, probable, and possible categories of osteoarticular TB out of 112 patients included in the study by CRS; gene Xpert result was positive in 35 out of the 37 different CRS categorized cases. Of the 112 cases, culture was put in 40 cases, and, of these cultures, 5 cases showed the growth of MTB. Of these, 4 cases were included in the 35 cases diagnosed by gene Xpert.

Smear microscopy was positive in 6 out of 37 CRS categorized cases. When compared with CRS, the sensitivity of gene Xpert assay, culture, and smear was found to be 94.6%, 13.5%, and 16.2%, respectively, while specificity in all the three types of tests was 100%. When kappa statistics were applied, the percentage of agreement gene Xpert, culture, and microscopy with CRS was found to be 95%, 20%, and 22.6%, respectively. Follow-up of the gene Xpert positive patients after getting anti-tubercular treatment revealed improved conditions.

CONCLUSION

Gene Xpert could detect 31 extra cases with a low and very low mycobacterial load that were missed by the routine culture methods. Hence, more samples should be processed for molecular diagnostic methods like gene Xpert along with other conventional methods for the validation of the molecular test prospectively for the timely diagnosis of osteoarticular TB.

Key Words: Tuberculosis; Extrapulmonary; Osteoarticular; Gene Xpert assay; Composite reference standard

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Core Tip: Osteoarticular tuberculosis (OATB) is a severe form of extrapulmonary tuberculosis (TB) that needs prompt management. However, there is difficulty in collecting samples and, secondarily, the paucibacillary nature of the lesion gives poor sensitivity and reproducibility, often with long turnaround time of the routine conventional laboratory tests. Xpert MTB RIF assay has been approved by the World Health Organization for rapid diagnosis of pulmonary/extrapulmonary TB. This study aims to find the diagnostic efficiency of gene Xpert for OATB in suspected patients. We found sensitivity of gene Xpert assay, culture, and smear when compared with CRS to be 94.6%, 13.5%, and 16.2%, respectively, while specificity in all the three types of tests was 100%. The kappa percentage of agreement for gene Xpert, culture, and microscopy were found to be 95%, 20%, and 22.6%, respectively. Follow-up of the gene Xpert positive patients after getting anti-tubercular treatment revealed improvement of their conditions. We conclude that gene Xpert has higher sensitivity than other conventional tests for the timely diagnosis of OATB.

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INTRODUCTION

Tuberculosis (TB) is among the top ten causes of mortality worldwide. In 2019, an estimated 10.0 million (range, 8.9–11.0 million) were affected with TB globally, of which 1.2 million died, including 208000 human immunodeficiency viruses (HIV)-positive patients[1]. Most people who developed TB in 2019 belonged to the World Health Organization (WHO) regions of South-East Asia (44%). India topped the list of eight high burden TB countries contributing to almost 26% of the global TB cases[1].

Primarily, it is a disease of the lower respiratory tract, but it can involve other organs with multitudinous presentations. It can be classified as pulmonary TB and extrapulmonary TB (EPTB), with the latter contributing to approximately 14% of all the reported TB cases[2]. Osteoarticular TB (OATB) is a form of EPTB that comprises 1%-4.3% of total tuberculosis cases and 10%-15% of all EPTB cases[3,4]. Osteoarticular involvement usually results from paucibacillary hematological dissemination and fixation of a colony of mycobacteria inside the active bone marrow. OATB can cause notable morbidity, and a high index of suspicion is required for prompt diagnosis to avoid unwanted sequelae[5,6]. OATB remains a significant problem worldwide, leading to severe deformities and functional disability due to difficulty in diagnosis and delay in the initiation of specific treatment. Moreover, India is an endemic focus of TB, where most orthopedic surgeons continue to practice diagnosing OATB solely on clinical and radiological findings and initiating empirical anti-TB treatment (ATT)[5-7]. This is partly attributed to the challenges faced in collecting the samples from the appropriate site (which at times are difficult anatomically) and the paucibacillary nature of lesion, causing poor sensitivity reproducibility and long turnaround time of the routine conventional laboratory tests and the requirement for invasive procedures and expertise[8]. Hence, there is a need for a molecular diagnostic test with a short turnaround time to diagnose OATB rapidly.

In 2010, the WHO recommended using Xpert MTB/RIF assay (Xpert) in pulmonary TB cases for concurrent diagnosis and rifampicin resistance of TB bacilli. WHO also contemplated the same for EPTB in the year 2013[9,10]. The automated Xpert MTB/RIF (Cepheid, Sunnyvale, CA, United States) assay is based on hemi-nested real-time polymerase chain reaction principle for the concurrent detection of MTB complex and RIF resistance[11]. The present study aims to estimate the efficacy of the gene Xpert assay for the precise diagnosis of OATB.

MATERIALS AND METHODS

This is a retrospective study conducted jointly by the Department of Microbiology and Orthopaedics at a tertiary center in eastern India. The study was conducted by analyzing the data of the gene Xpert assay and follow-up data of patients spread over a 3-year duration from January 2018 to February 2021. Clinical specimens of 112 OATB TB cases were received for diagnosis of TB by the Gene-Xpert-MTB-Rif assay. A part of the sample was processed according to the standard protocol of gene Xpert and subjected to the assay[11]. Tissue samples were cut into small pieces followed by crushing, mixing with buffer, and then vortexing for homogenization. Samples were then incubated for 15 min or more till the tissue was dissolved and centrifuged at 3000 rpm; the supernatant was used for the assay. Synovial fluid and pus samples were also processed according to standard protocol. Cartridges were put inside the device for extraction of DNA and simultaneous amplification of *rpoB* gene (192bp) and generation results[11]; the remaining part of the samples was subjected for smear microscopy by Ziehl-Neelsen stain. Forty samples were subjected to culture. The demographic details and part of involvement were retrieved from files in the medical records. A follow-up telephonic survey of the health status survey, including compliance to ATT, using short form survey-12 free online calculator was performed by one of the researchers (Jain M)[12].

Composite reference standard (CRS) was taken into account to evaluate the diagnostic efficacy of the different test methods used in the study. According to CRS, patients were categorized into four groups: (1) confirmed OATB cases (culture-positive); (2) probable OATB cases (culture-negative but gene Xpert positive, and the patient responded well to anti-TB therapy); (3) possible OATB cases (condition improved after getting anti-TB therapy and had radiographic findings consistent with OATB but lack of bacteriological evidence); and (4) non-TB (culture and all other tests for TB were negative, and the patient improved without getting any anti-TB treatment)[13-15].

The data were entered into a Microsoft Office Excel sheet. The sensitivity, specificity, positive predictive value, and negative predictive value were calculated to evaluate the diagnostic performance of gene Xpert assay and microscopy against the culture method. Kappa statistics was applied to derive the percentage of agreement between gene Xpert and culture.

RESULTS

Synovial fluid was the most common sample (86/112) received in the laboratory. The other samples included tissues of the intervertebral disc and bone fragments ($n = 11/112$) and aspirated pus ($n = 25/112$). All 112 samples were subjected to smear microscopy and CBNAAT by gene Xpert MTB-Rif assay, and 40 samples were put on culture. According to CRS, 5 cases were confirmed to have OATB; of the 35 gene Xpert positive cases, 31 belonged to the probable OATB category, and 1 showed improvement after getting ATT despite being culture. Gene Xpert negative belonged to possible OATB category. Of the 112 samples, 35 samples were positive for MTB complex by gene Xpert. Smear microscopy was positive in 6 cases; all of these were detected by gene Xpert and culture was positive in 5 cases; of these, 4 were also positive by gene Xpert (Table 1).

The study population aged between 10-60 years. However, most of the cases (27.0%) confirmed OATB belonged to age group 21-30 years (Table 2). The positivity rate was equal for gender (male: female = 51.4%: 48.6% (Table 2). The spine was the most common confirmed site involved, followed by the knee, as shown in Table 3. The duration of the illness in the confirmed cases varied from 1-12 mo. All the cases were human immunodeficiency virus-negative.

Of the 35 gene Xpert confirmed cases, smear microscopy was positive only in 6 cases where MTB was detected in the range of low; in the remaining 29 cases, the detection of MTB was very low. None of the cases were resistant to rifampicin. Of the 35 cases, 18 cases could be followed up with clinical outcome and treated with ATT, and these 18 cases responded to standard combination ATT (Table 1).

Sensitivity of Xpert assay, culture, and smear, when compared with CRS, was found to be 94.6%, 13.5%, and 16.2%, respectively; specificity in all three types of the test was found to be 100%. When kappa statistics were applied, the percentage of agreement among Gene Xpert, culture, and microscopy with that of CRS was found to be 95.0%, 20.0%, and 22.5%, respectively (Table 3).

Table 1 Categorization of cases according to composite reference standard

Cases	Smear microscopy	Culture	Gene Xpert	ATT course (in mo)	Outcome (SF-12)		CRS category
					PCS-12	MCS-12	
Case No. 1	Negative	No growth	Positive	12	48.76	55.50	Probable OATB case
Case No. 2	Negative	Positive	Positive	Lost to follow-up			Confirmed OATB case
Case No. 3	Negative	No growth	Positive	15	46.03	56.9	Probable OATB case
Case No. 4	Negative	No growth	Positive	Lost to follow-up			Probable OATB case
Case No. 5	Negative	No growth	Positive	Lost to follow-up			Probable OATB case
Case No. 6	Positive	No growth	Positive	Lost to follow-up			Probable OATB case
Case No. 7	Negative	No growth	Positive	24	56.57	60.75	Probable OATB case
Case No. 8	Negative	No growth	Positive	24	46.03	56.9	Probable OATB case
Case No. 9	Negative	No growth	Positive	6	48.60	33.57	Probable OATB case
Case No. 10	Positive	No growth	Positive	Lost to follow-up			Probable OATB case
Case No. 11	Negative	No growth	Positive	Lost to follow-up			Probable OATB case
Case No. 12	Negative	No growth	Positive	Lost to follow-up			Probable OATB case
Case No. 13	Negative	No growth	Positive	Lost to follow-up			Probable OATB case
Case No. 14	Positive	No growth	Positive	Lost to follow-up			Probable OATB case
Case No. 15	Positive	Contamination	Positive	Lost to follow-up			Probable OATB case
Case No. 16	Negative	Contamination	Positive	Lost to follow-up			Probable OATB case
Case No. 17	Negative	No growth	Positive	6	56.57	60.75	Probable OATB case
Case No. 18	Negative	No growth	Positive	Lost to follow-up			Probable OATB case
Case No. 19	Negative	No growth	Positive	6	52.23	56.51	Probable OATB case
Case No. 20	Negative	No growth	Positive	21	52.23	56.51	Probable OATB case
Case No. 21	Negative	No growth	Positive	15	52.23	53.63	Probable OATB case
Case No. 22	Positive	Contamination	Positive	12	56.57	60.75	Probable OATB case
Case No. 23	Negative	No growth	Positive	15	48.60	33.57	Probable OATB case
Case No. 24	Negative	No growth	Positive	Lost to follow-up			Probable OATB case
Case No. 25	Positive	Positive	Positive	Lost to follow-up			Confirmed OATB case
Case No. 26	Negative	No growth	Positive	12	51.81	48.67	Probable OATB case
Case No. 27	Negative	Positive	Positive	12	48.76	55.50	Confirmed OATB case
Case No. 28	Negative	No growth	Positive	6	56.57	60.75	Probable OATB case
Case No. 29	Negative	No growth	Positive	Lost to follow-up			Probable OATB case
Case No. 30	Negative	No growth	Positive	12	51.81	48.67	Probable OATB case
Case No. 31	Negative	No growth	Positive	Lost to follow-up			Probable OATB case
Case No. 32	Negative	No growth	Positive	12	40.76	40.94	Probable OATB case
Case No. 33	Negative	No growth	Positive	Lost to follow-up			Probable OATB case
Case No. 34	Negative	Positive	Positive	2	28.93	40.32	Confirmed OATB case
Case No. 35	Negative	No growth	Positive	1.5	28.93	40.32	Probable OATB case
Case No. 36	Negative	Positive	Negative	12	48.76	55.50	Confirmed OATB case
Case No. 37	Negative	No growth	Negative	1.5	28.93	40.32	Possible OATB case

CRS: Composite reference standard; ATT: Anti-tuberculosis treatment; OATB: Osteoarticular tuberculosis; SF-12: Short form survey-12; PCS-12: Physical composite scale-12; MCS-12: Mental health composite scale-12.

Table 2 Demographic and clinical distribution of composite reference standard positive, probable and possible osteoarticular tuberculosis cases, n (%)

Characteristics		Cases (n = 37)
Age group (yr)	0 - 10	1 (2.7)
	11 - 20	5 (13.6)
	21 - 30	10 (27.0)
	31 - 40	6 (16.2)
	41- 50	6 (16.2)
	51 - 60	6 (16.2)
	> 60	3 (8.1)
Sex	Male	19 (51.4)
	Female	18 (48.6)
Site if OATB	Knee	8 (21.6)
	Spine	20 (54.1)
	Elbow	1 (2.7)
	Wrist	1 (2.7)
	Psoas abscess	7 (18.9)

OATB: Osteoarticular tuberculosis.

Table 3 Performance assay and statistical analysis of gene Xpert, culture and, smear microscopy against composite reference standard (n = 40)

Methods	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Kappa statistics (% agreement)
Gene Xpert	94.6	100.0	94.6	100.0	95.0
Culture	13.5	100.0	13.5	100.0	20.0
Smear microscopy	16.2	100.0	16.2	100.0	22.5

PPV: Positive predictive value; NPV: Negative predictive value.

DISCUSSION

OATB remains a nuisance as the provenance of functional disability, which could lead to severe deformities and cause lifetime stigma. Therefore, making an early diagnosis and treatment is imperative to avoid unacceptable consequences. India is one of the high burden TB countries where many orthopedic surgeons diagnose OATB by relying on clinical and radiological findings and start ATT empirically[5].

The incidence of OATB ranges from 1.0%-4.3% of all TB cases and comprises 5-15% of all EPTB[5,14-16]. In a study by Gogia *et al*[5], 16 cases out of 120 were diagnosed with OATB over 3 years. However, Muangchan *et al*[7] reported 99 cases of OATB during a 2 year period, which seems to be quite a high number. In the present study, 37 cases were proven of the 112 cases (33.03%) to have OATB after a retrospective analysis of 3 years of data, similar to the study by Yoon *et al*[16].

Enache *et al*[8], in their study on EPTB, found that two-third of patients were older than 40 years. In some other studies, the median age was reported in the higher range of 50-60 years[9,13]. However, in our study, maximum cases belonged to the younger age group; the highest was in the 21-30 age group (27.0%). Female predominance was observed in some studies[7,16], and in others, the maximum cases were males[5,8]. In our study, it was almost equally distributed. Clinically, pain is the most common

symptom[7], which was the finding in our study also.

The spinal area was the most common (54.1%) site affected in our study, followed by knee joint and psoas abscess (21.6% and 18.9%, respectively), which is in concordance with several other studies with a preponderance of spinal involvement[3,17].

Yoon *et al*[16], in their study, observed that there are limited diagnostic options for EPTB, which led them to analyze retrospectively the different spectrums of EPTB regarding clinical patterns, underlying diseases, and diagnostic methods. Synovial fluid or any drained purulent fluid from the suspected lesion site can be examined for acid-fast bacteria (AFB) in cases of OATB. A direct smear of the sample can show positivity for AFB in as low as 27% of cases[17]. Six out of 35 gene Xpert confirmed cases in our study were AFB positive. Low positivity in OATB may be due to the paucibacillary nature of the lesion[18]. Culture on various specimens like a biopsy, cold abscess, or synovial fluid is considered the standard gold method for diagnosis[17]. A lower range of culture positivity has been observed in different studies, such as 11.2% and 19.2 % by Yoong *et al*[16] and Muangchan *et al*[7]. However, a higher positivity (63%) was seen in the review article by Haider *et al*[17].

In our study, we also found a lower culture positivity rate (13.7%) in samples subjected for culture, which could be due to a less amount of such samples, as the maximum amount was subjected for gene Xpert. The long turnaround time and the possibilities of contamination were the major disadvantages of the conventional culture technique. Similarly, the microscopy method also has the drawback of lack of reproducibility and low reliability, particularly in EPTB cases with a low bacterial load[18-20]. Molecular tests like gene Xpert, on the other hand, have the advantage of short turnaround time, which can help the physician determine the correct management of cases[21]. In the present study, the sensitivity, specificity, and percentage of agreement compared with CRS of gene Xpert were similar (94.6%, 100%, and 95%, respectively)[22]. These results may be because fewer samples were put in culture, and the statistical analysis was made using those small proportions of samples; in addition, the sample size was also less. Despite the statistical values, it cannot be ignored that the gene Xpert could detect 31 extra cases with low and very low bacterial load, which were missed by the culture methods. All the cases detected by gene Xpert were sensitive to rifampicin, and the clinical outcome was favorable.

Since this is a retrospective study and not all samples were processed for culture, accurate analysis of all the samples could not be done, which is the limitation of our study. Moreover, clinical data were retrieved from the database, and some patients were lost to follow-up; if the follow-up data of all the patients had been included in the present study, then the utility of the molecular methods could have been more established.

CONCLUSION

Hence, to conclude, conventional diagnostic methods such as smear are done everywhere for mycobacterium TB diagnosis, but this test is negative in most orthopedic cases. Therefore, more samples should be processed using molecular diagnostic methods like gene Xpert along with other conventional methods in order to validate the molecular test prospectively for the timely diagnosis of OATB. When more cases can be diagnosed early and treatment initiated at the right time, the likelihood of cure is greater and the severe consequences of the disease can be prevented.

ARTICLE HIGHLIGHTS

Research background

Tuberculosis (TB) is among the top ten causes of mortality worldwide. In 2019, an estimated 10.0 million were affected with TB globally, of which 1.2 million died. India topped the list of eight high burden TB countries, which contribute to almost 26% of the global TB cases. Osteoarticular tuberculosis (OATB) is a form of extrapulmonary TB that comprises 1.0%-4.3% of total tuberculosis cases and 10%-15% of all extrapulmonary TB cases. OATB remains a significant problem worldwide, leading to severe deformities and functional disability due to difficulty in diagnosis and delay in the initiation of specific treatment. Moreover, India is an endemic focus of TB, where most orthopedic surgeons continue to practice diagnosing OATB solely on clinical and radiological findings and initiating empirical anti-TB treatment.

Research motivation

There is a need for a molecular diagnostic test with a short turnaround time to diagnose OATB rapidly. In 2010, the World Health Organization recommended using Xpert MTB/RIF assay in pulmonary TB cases for concurrent diagnosis and rifampicin resistance of TB bacilli.

Research objectives

The objective is to estimate the efficacy of gene Xpert assay for the precise diagnosis of OATB.

Research methods

This retrospective study was conducted by analyzing the data of the gene Xpert assay over a 3-year period. The diagnostic efficiency of gene Xpert was evaluated against the composite reference standard.

Research results

A total of 37 cases fell into positive, probable, and possible categories of OATB out of 112 patients included in the study by composite reference standard; gene Xpert result was positive in 35 out of the 37 different composite reference standard categorized cases. Follow-up of the gene Xpert positive patients after getting anti-tubercular treatment revealed improved conditions.

Research conclusions

Conventional diagnostic methods such as smear are done everywhere for mycobacterium TB diagnosis, which is negative in most orthopedic cases.

Research perspectives

More samples should be processed for molecular diagnostic methods like gene Xpert along with other conventional methods for the validation of the molecular test prospectively for the timely diagnosis of osteoarticular TB.

FOOTNOTES

Author contributions: Mohanty M and Mishra B conceived the idea; Jain M created the proposal and Mishra B received the clearance; Mohanty M and Puthiyapura LK collected the data; Jain M and Mohanty M wrote the paper; Mishra B and Puthiyapura LK revised the manuscript for important intellectual content; All authors have read and agreed to the content of the manuscript.

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