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Original Research Article

INDEX guidelines for extra-pulmonary tuberculosis: knowledge and practice among clinicians in Bengaluru, Karnataka

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ABSTRACT

Background: Extra-pulmonary tuberculosis (EPTB) remains a major problem in developing countries, which acquire diagnostic and management challenges. The study was conducted to characterize the diagnosed EPTB cases, and to understand the perspectives of clinicians on diagnosis and challenges in its management.
Methods: A total of 150 EPTB patients' medical records were reviewed at two tertiary hospitals in Bengaluru, Karnataka for the period January 2017 to December 2017. The questionnaire-based interview was conducted among clinicians (n=42) during the study period.
Results: The mean age and weight of EPTB patients (females (77, 51%) and males (73, 49%) were 32.5 (±17.5) years and 44.5 (±16.3) kilograms, respectively. Pleural TB (44, 29%), cervical lymph node TB (LNTB) (32, 21%) and abdominal TB (17, 11%) were the most common sites of EPTB involvement, followed by bones and joints TB (11, 7%), spine TB (10, 7%), hilar/mediastinal TB (9, 6%), tuberculoma (8, 5%), TB meningitis (6, 4%), abdominal LNTB (6, 4%), urinary TB (4, 3%) and others (3, 2%). We found GeneXpert was the basis of EPTB diagnosis in 43.3% of cases followed by acid-fast bacilli (AFB) smear microscopy (20.7%) and culture (12.5%). Of 150 EPTB suspected cases, 73% (110) were started anti-TB treatment (ATT), including 8% (12) having received ATT previously. According to LIKERT scale options, 90% of clinicians agreed GeneXpert as a promising diagnostic tool for diagnosis as compared to other microbiological (79%) and histopathological tests (55%).
Conclusions: The quality of EPTB diagnosis and management practices at these institutions is satisfactory according to the principles laid down in INDEX TB guidelines or the national guidelines.

Keywords: Awareness, Diagnosis, Extra-pulmonary tuberculosis, Tertiary healthcare facilities

INTRODUCTION

Globally, tuberculosis (TB) remains a major infectious disease accounting for nearly 10.4 million incident cases in 2019; and 1.2 million deaths among human immunodeficiency virus (HIV) negative people and 208,000 deaths among HIV positive patients.[1] India is one of the high TB burden country and accounts for 2.64 million TB cases, thus contributing approximately 26% of the world's burden.[2] According to the clinical manifestations, TB can be divided into two types (i) Pulmonary TB (PTB) and (ii) Extra-pulmonary TB

(EPTB). PTB affects lungs and EPTB involves in other parts of the body except lungs. EPTB cases accounts for 15-20% of reported incident TB cases, worldwide and in India, it accounts for 27% (640,399 of the 2,404,815) of all notified TB cases (TB India report 2020).[3]

In the past few decades, the proportion of EPTB has increased remarkably and diagnosis remains a challenge due to its inherent paucibacillary nature, the non-availability of diagnostic facilities at the primary and secondary health facilities and due to non-specific presentation of the disease.[4,5] An high index of suspicion and clinical acumen is needed among the clinicians for early detection of EPTB cases; in addition, knowledge of appropriate and methodical use of available diagnostic modalities in a cost-effective manner and in-depth knowledge on varying sensitivity and specificity of different diagnostic tools remains crucial for the diagnosis.

In India, varying practices are prevalent among clinicians for diagnosis and management of EPTB patients. A study by Sharma et al. has facilitated the formulation of guidelines for suspecting, diagnosing and managing EPTB at all levels of healthcare delivery.[6]

Over the years, to address the dilemma and non-uniformity among practitioners the National TB Elimination Programme (NTEP) has formulated and developed guidelines such as Standards for TB Care in India (2014), TB Technical and Operational Guidelines (2016), Programmatic Management of drug-resistant TB (2019) and INDEX TB guidelines (2017). The INDEX TB guidelines is focussed on EPTB exclusively and provide guidance on appropriate management of the disease, it is based on ten principles that emphasize on improved case detection, appropriate care and reporting of treatment outcome of EPTB patients.[6-9]

In India, there are seldom any studies or evidence that measures the understanding and the level of its application especially at tertiary health care facilities where majority of EPTB cases are detected. It is prudent for the programme to assess and initiate appropriate timely measures to improve the quality of EPTB diagnosis and its implementation at the health facilities. We conducted a study at two tertiary hospitals of Bengaluru, South India with a broad aim to understand the extent of adherence to the principles of INDEX TB Guidelines for diagnosis and treatment of EPTB patients and to assess the knowledge of health care providers with regards to the diagnosis and management of EPTB.

The objectives of our study were to (1) to determine the proportion of EPTB patients diagnosed according to the principles of INDEX TB Guidelines, (2) To determine the proportion of EPTB patients treated as per the recommendations of INDEX TB Guidelines and (3) To explore the challenges faced by treating clinicians for appropriate care and management of EPTB.

METHODS

Study design and population

A cross-sectional study was conducted at ESIC Medical College and PGIMSR and St. Martha's hospital in Bengaluru, Karnataka between January and December 2017. The study population comprised of all the EPTB patients diagnosed during the study period based on records and the treating clinicians directly involved in management of EPTB cases.

Study settings

The study was conducted at two sites of Bengaluru city, Karnataka. The ESIC Medical College and PGIMSR is a Government tertiary care hospital and has nearly 550 beds; it caters to insured persons and provides services to patients on outpatient and inpatient basis. It has most of the general and specialized services needed for the patients and treats at least 300,000 patients annually. The St.Martha's hospital is a missionary hospital and is one of the oldest hospital in Bengaluru with 550 beds and caters to general public. The hospital has all the broad and specialized patient care services and provides services to at least 250,000 patients annually.

Management of TB cases at study sites: The NTEP has established a designated microscopy centre and the presumptive TB cases identified at the different departments in the hospitals are further evaluated with smear microscopy, chest X-ray, cytology, histopathology, magnetic resonance (MRI), computed tomography (CT) scan, ultrasonography (US) and endoscopy based on the clinicians decision of investigation. The samples that necessitates the investigation of GeneXpert, Mycobacterial Growth Indicator Tube (MGIT) culture and Line Probe Assay (LPA) are referred to the programme identified facilities outside the hospital. Based on the results, the patients are managed according to the standard programme guidelines.

Data collection

A data collection format was developed and two trained researchers from National Tuberculosis Institute (NTI), Bengaluru collected the information from the medical records department. For objectives 1 and 2: The following variables were extracted from the records: age, sex, weight, clinical presentation and duration of symptoms, EPTB types and diagnostic tools used to detect EPTB. Further exploration were made in the clinical case sheets to review all EPTB patients diagnosed and/or treated in hospitals during the period January to December 2017 (Table 1).

For objective 3: A semi-structured questionnaire with LIKERT scale options was developed to assess the knowledge and to identify the challenges faced by the treating clinicians for management of EPTB cases.

The questionnaire was pilot tested before administering to the select treating clinicians who were directly involved in management of EPTB cases after obtaining their written informed consent.

Table 1: Record review of all EPTB patients diagnosed and/or treated in hospitals during the period January 2017 to December 2017.

Variables	Response
Microbiological confirmation advised?	Y/N/NA
If microbiological test advised, was it the appropriate test?	Y/N
Histopathology advised?	Y/N
If histopathological test advised, was it appropriate for the type of EP-TB being diagnosed?	Y/N
Whether basis of diagnosis stated (microbiologically/clinically diagnosed)?	Y/N
Whether diagnosis based on non-approved tests such as serology, IGRA	Y/N
Whether screened for pulmonary TB? ***(*Screening will deem to have been done if presence/absence of pulmonary symptoms has been recorded and/or chest x-ray undertaken irrespective of the organ effected)***	Y/N
Whether given Trial ATT	Y/N
Whether classified as new/previously treated/DR-TB	Y/N
Whether appropriate specimen subjected to drug sensitivity testing from a RNTCP certified laboratory, wherever required?	Y/N
Whether regimen prescribed as per guidelines for new, previously treated and PMDT?	Y/N
Whether anti-TB treatment initiated within one week of diagnosis?	Y/N
Whether any ancillary medications were prescribed as per the guidelines, wherever required?	Y/N
Whether tested for HIV?	Y/N
If HIV reactive, whether given CPT?	Y/N
If HIV reactive, whether given ART?	Y/N
Whether screened for diabetes?	Y/N
If diabetic, whether on anti-diabetic treatment during ATT?	Y/N
Whether screened for current tobacco use?	Y/N
Whether screened for current alcohol use?	Y/N
If yes, whether given cessation advice / linked to de-addiction center?	Y/N
Whether referred to the health center nearest to patients' home for continuation of ATT?	Y/N
Whether notified?	Y/N
If notified whether public health action was provided by the RNTCP?	Y/N
If treatment continued in tertiary care facility:	Y/N
Whether initial home visit documented?	Y/N
Whether the duration of treatment as per guidelines?	Y/N
Whether treatment was directly observed/ICT Based as per guidelines?	Y/N
Whether retrieval actions on interruption of treatment documented?	Y/N
Whether treatment outcome documented?	Y/N
Whether follow up during treatment carried out as per guidelines?	Y/N

[#]Y, Yes; N, No and NA, Not applicable

Questionnaire was framed to understand the knowledge and its application on (1) Diagnosis of EPTB: areas related to radiological services, biochemical investigations, cytology of body fluids or aspirates, histopathological examination of biopsy samples, serological tests, mantoux test, microbiological investigations and rapid molecular diagnostic tests (2) Treatment modalities of EPTB: Awareness of regimen, duration of treatment, monitoring methods, follow-up, national guidelines for diagnosis and management of EPTB cases and notification of EPTB (3) NTEP certified TB laboratories: Availability of NTEP certified laboratory services for TB diagnosis within the premises and the mechanism of referral for examination of specimen from extra-pulmonary sites.

RESULTS

A total of 150 EPTB patients were included in the study; of which 90 (60%) were diagnosed from ESIC Medical College and 60 (40%) were from St. Martha's Hospital, Bengaluru.

Characteristics of diagnosed EPTB patients

Of all the EPTB patients, 77 (51%) were females and 73 (49%) were males. The mean age was found to be 32.5 (±17.5) years and mean weight was 44.5 (±16.3) kilograms (Table 2).

Table 2: Sociodemographic characteristics of EPTB patients (n=150).

	Years	Male N (%)	Female N (%)
Age group (years)	≤14	15 (10.0)	14 (9.3)
	15-29	17 (11.3)	24 (16)
	30-44	22 (14.7)	15 (10)
	45-59	18 (12)	16 (10.7)
	≥60	1 (0.7)	8 (5.3)

Site of EPTB: Majority of the patients were diagnosed with pleural TB, 44 (29%) followed by cervical lymph node TB, 32 (21%); abdominal TB, 17 (11%); bones and joints TB, 11 (7%); spine TB, 10 (7%); hilar or mediastinal TB, 9 (6%); tuberculoma, 8 (5%); TB meningitis, 6 (4%); abdominal LNTB, 6, (4%); urinary TB, 4 (3%) and others 3 (2%) (Table 3).

Table 3: Types and proportion of EPTB diagnosed in the two hospitals (n= 150).

Type of EPTB	N (%)
Pleural TB	44 (29)
Cervical LNTB	32 (21)
Abdominal TB	17 (11)
Bone and joint TB	11 (7)
Spine TB	10 (7)
Hilar/mediastinal LNTB	9 (6)
Tuberculoma	8 (5)
TB meningitis	6 (4)
Abdominal LNTB	6 (4)
Urinary TB	4 (3)
Others	3 (2)

Turnaround time: For 61 (41%) patients, the mean turnaround time for the diagnosis after visit to hospital was 6 days (range: 0 to 78 days).

Close contact and previous history of TB: About 27 (18%) of patients had history of close contact with TB cases and 12 (8%) had received anti-tuberculosis treatment previously.

Drug susceptibility testing: About 82 (55%) patients samples were subjected to drug susceptibility testing (DST) against first-line drugs. Of the 82 samples, 10 (8%) were found to be drug-resistant.

HIV screening: The screening for HIV revealed that 93 (62%) of patients were screened for HIV and the remaining 57 (38%) did not know their HIV status; among those screened 8 were found to be reactive to HIV.

Mode of EPTB diagnosis

All 150 patients' samples were subjected to smear microscopy followed by GeneXpert (n=60, 40%) and MGIT culture (n=32, 21%). We found GeneXpert findings consistent with EPTB in 43.3% of cases followed by acid-fast bacilli positive in smear microscopy (21%) and culture (13%) (Table 4).

Table 4: Diagnosis of EPTB (n=150).

Diagnostic tests	Sample tested (N)	Positives N (%)
AFB smear	150	31 (20.7)
MGIT culture	32	4 (12.5)
GeneXpert	60	26 (43.3)
Total microbiologically confirmed	150	47 (31.3)

Off the presumptive EPTB patients (n=150) a total of 110 (73%) were offered tissue-based diagnosis as ancillary tests which included cytology, histopathology and biochemical tests, in addition to radio imaging and Mantoux test to aid clinical diagnosis of EPTB (Table 3). EPTB was clinically diagnosed in 116 out of 150 cases (Figure 1).

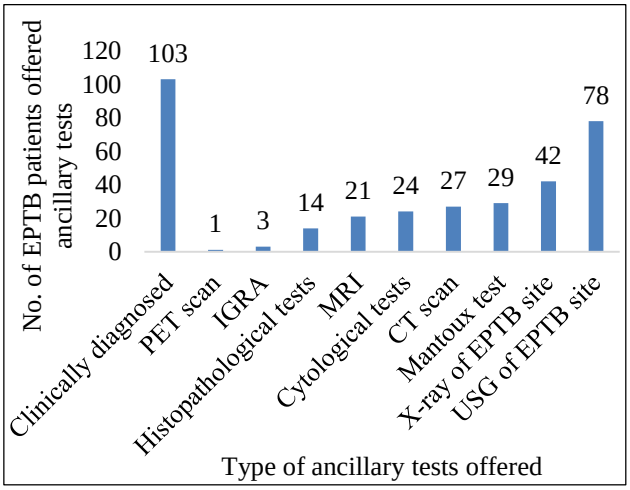

Figure 1: Presumptive EPTB patients subjected to ancillary tests to aid clinical diagnosis of EPTB (n=150).

Assessment of EPTB diagnosis knowledge among health care providers

A self-administered questionnaire was provided to 42 health care providers working in various clinical departments at both the study sites. The health care providers included clinicians from department of general medicine (43%), paediatrics (19%) and orthopaedics (17%) (Table 5).

Knowledge on EPTB diagnosis, treatment and NTEP certified laboratories

Majority of the clinicians had good working knowledge on the modalities of diagnosis, treatment and NTEP certified laboratories for referrals. The study findings

revealed that 90% of clinicians agreed GeneXpert was a promising method for EPTB diagnosis, followed by other microbiological tests (79%), histopathological tests (55%) and serodiagnostic tests (38%). About 88% opined that further evaluation to diagnose pulmonary TB is essential. Majority (95%) agreed that all EPTB cases should be notified to public health authorities and some clinicians believed that it's only required if they initiate treatment for patients.

Table 5: The category of clinicians.

Clinicians	N	%
SR (Medicine)	18	43
SR (Paediatrics)	8	19
SR (Orthopaedics)	7	17
Others (Professors)	9	21

SR: Senior Residents

However, the challenges encountered by the treating clinicians were non-availability of instant transportation of tissue samples to the certified laboratories outside the hospital campus for further testing and lack of personalized communication from the laboratories on the results of their patients.

DISCUSSION

It is one of the few studies conducted to assess the knowledge and the challenges involved in the management of EPTB cases at tertiary health facilities in South India. We explored the awareness, practice and diagnostic challenges in management of EPTB among treating clinicians. Our study findings reveal that despite the efforts made by the programme all these years, the management of EPTB patients at tertiary health facility needs further strengthening. We highlighted the importance of health care workers in understanding the various presentations of EPTB and selection of appropriate diagnostic tools that could reduce the diagnostic delay. This study highlighted the importance of early diagnosis of EPTB and guided clinicians to choose appropriate recommended treatment regimens for EPTB. We also showed good adherence to the principles for the diagnosis and the challenges among clinicians according to the national EPTB management guidelines.

In this present study, our results showed that the group of EPTB patients were young, mean age 32.5 years (SD±17.5) and weight was 44.5 kg (SD±16.3 kgs). Similarly, a south Indian study from our geographical area, Karnataka, observed that EPTB was more common among productive age group (15-44 years, 50.95%).[10] Our results are consistent with previous studies from Nepal, Ethiopia, Saudi Arabia, United States and Morocco. A study from Nepal by Sreeramareddy et al suggested that younger age group (< 25 years, 40.9%) were associated with EPTB relative to PTB.[11] Arega et al from Ethiopia found that EPTB patients were relatively young (mean age 32 years) and a Saudi Arabian study reported the high prevalence of EPTB among protective age groups.[12,13] A study by Peto et al from United States reported that the EPTB patients were slightly higher in younger (Mean 44) than that of patients with PTB and Sbayi et al from Morocco reported that the average age of EPTB patients was 31.74±18.83 years (median age of 26).[14,15] In contrast, studies from USA and Turkey observed that EPTB was not associated with younger age.[16,17]

Studies have suggested that sites of EPTB may vary according to geographical location and population.[18] In India, pleural effusion and peripheral lymph node TB are the two commonly encountered forms of EPTB.[6,19] In our study, we found that the majority of the EPTB samples were collected from Pleural TB (n=44, 29%) followed by cervical LNTB (n=32, 21%), abdominal TB (n=17, 11%) and bones and joints TB (n=11, 7%). Pleural TB is the most common manifestations of EPTB and India accounts for 30 to 80% of pleural effusion.[21] Prakasha et al from Karnataka reported that plural TB was common form of EPTB (28.03%) followed by lymph node TB (24.81%).[10] A study from North India by Chander et al showed that pleural TB was found to be most common (61.6%) followed by lymph node TB (23.2%) and abdominal TB (9.3%).[22] A study from China by Kang et al observed that tuberculous pleurisy (50.15%) was most common EPTB, followed by bronchial tuberculosis and tuberculous lymphadenitis.[21] In contrast, Arega et al from Ethiopia observed that Tubercular lymphadenitis (TBLN) is the most common form of EPTB followed by abdominal TB.[12]

Several studies have reported many risk factors for the development of EPTB and one of the key factors is compromised host immunity.[23] EPTB was reported most commonly in HIV patients, particularly in those with low CD4 cell counts. In our present study, 93 (62%) of patients were screened for HIV and 8 were found to be HIV positive. We observed that 93% of clinicians agreed that all patients diagnosed with EPTB should be screened for HIV and 88% opined that further evaluation to diagnose pulmonary TB is essential. According to previous reports, about 10 to 100% of EPTB patients were found to be associated with PTB.[21,24-26] A study from Kang et al observed that 65.31% tuberculous pleurisy and 62.64% tuberculous meningitis were associated with PTB, respectively.[21] Hence, as suggested by our clinicians we strongly recommend that most of the suspected EPTB cases should be screened for concomitant pulmonary involvement in order to aid early diagnosis, proper classification and prompt management of such patients who are much more infectious than those suffering only from EPTB.

The knowledge assessment of health care providers on EPTB diagnosis led to an observation that majority of clinicians agreed GeneXpert as a promising diagnostic method compared to other microbiological tools, histopathological and serodiagnostic tests. Though less

than a third agreed serodiagnostic tests have a role in TB diagnosis, this reflects a knowledge gap as serodiagnostic tests have been banned in India since 2012 following the WHO policy statement for non-usage on serodiagnostic tests for diagnosis of both PTB and EPTB in 2011. Although culture-based TB diagnosis is still considered a gold standard, culture is time-consuming and requires appropriate infrastructure and expertise. Similarly, though AFB smear is very rapid and cost-effective, the differentiation between *Mycobacterium tuberculosis* (MTB) and non-tuberculous mycobacteria (NTM) is limited and the sensitivity varies considerably from 20 to 80%. To overcome such limitations; GeneXpert, a fully automated real-time semi-nested PCR endorsed by the WHO is a rapid molecular diagnostic tool for the diagnosis of both PTB and EPTB.[27] The GeneXpert is used for the detection of MTB and rifampicin resistance related mutations. Previous studies have reported that the sensitivity and specificity of AFB smear microscopy are lesser than GeneXpert in the diagnosis of both PTB and EPTB.[15] However studies have reported that GeneXpert cannot be recommended to replace standard conventional tests for EPTB diagnosis.[28] A study from Allahyartorkaman et al reported that sensitivity (76.5%) and specificity (95.9%) of GeneXpert for diagnosing EPTB is highly variable when compared with PTB diagnosis (sensitivity, 95.5% and specificity, 96.7%).[29] Although, GeneXpert is found to be promising for EPTB diagnosis, we strongly recommend that GeneXpert negative samples should be subjected to culture to rule out EPTB.

The study had few limitations. The sample size was relatively small and restricted to one city and findings cannot be generalized to all the healthcare settings in India. Also, we were not able to record the outcomes of EPTB patients, including those who were found to be negative by diagnostic tests.

CONCLUSION

The quality of EPTB diagnosis and management practices at these institutions is good and being practiced according to the principles laid down in INDEX TB guidelines or the national guidelines. The programme should facilitate or integrate diagnostic services to aid microbiological confirmation in EPTB samples and widely disseminate knowledge and information on the various presentations of EPTB, their diagnosis and treatment with a focus on clinicians of tertiary care hospital settings to enable them to make timely and informed decision on EPTB management.

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