

# Pattern, Diagnosis and Treatment Outcome of Extra Pulmonary Tuberculosis

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SR RI conceived idea, SR RI MKM drafted the study, SR collected data, SR RI SS did statistical analysis & interpretation of data, RI MKM SS critical reviewed manuscript, All approved final version to be published

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The Authors declares that there is no conflict of interest.

## Abstract

**Background:** Extra-pulmonary TB (EPTB) is a type of infection that may occur in any organ of the body other than lung. The disease most often remains undiagnosed or even untreated due to prime difficulty with specimens because they yield very few bacilli and hence associated with low sensitivity of acid-fast bacilli in smear and culture.

**Objective:** To study different diagnostic techniques such as smear, culture, histopathology, X-ray, MRI and CT scan for detection of EPTB, with its most common sites along with treatment outcome among patients visiting tertiary care setting.

**Methodology:** This descriptive study was undertaken at PHRC TB Research Centre Mayo Hospital Lahore during January 2016 to August 2017. After taking an informed consent a semi structured questionnaire was used to collect basic information, history, site of infection and treatment categories etc. Patients were followed up till completion of treatment.

**Results:** A total of 2096 patients were registered of which EPTB were 718 (35.6%) however 687 patients were included in final analysis. Chronic lymph node was the predominant type 280 (40.7%), followed by pleural fluid TB (20.8%), intestinal TB (17.3%) and spinal TB (8.9%). Diagnostic approaches for EPTB includes AFB smear & culture (9.5%), histopathology or cytology (60.9%), X-ray (3.6%), ultrasound (10.1%), magnetic resonance imaging 6.7% and computed tomography scan (9.0%), 60.9% patients showed excellent compliance, while 3.5% defaulted.

**Conclusion:** Lymph node TB remained predominant, good compliance and treatment outcome was observed among patients with EPTB.

**Key words:** Tuberculosis; Extra pulmonary TB; X-ray; Diagnosis

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## Introduction

**T**uberculosis (TB) is a major public health problem caused by *Mycobacterium tuberculosis*. Extra-pulmonary TB (EPTB) is a type of infection that may occur in any organ of the body other than lung. It is multi-systemic disease that may affect almost any organ such as lymph nodes, genitourinary tract, central nervous system (CNS), abdomen (intra-abdominal organs, peritoneum), pericardium, bone, joint and breast tuberculosis.

Miliary tuberculosis or disseminated tuberculosis is a type of infection which occurs in different organs at the same time such as kidneys, liver and spleen.<sup>1</sup>

Extra-pulmonary TB becomes life threatening at times such as TB meningitis and TB pericarditis while others cause eternal disability and significant ill-health. Prevalence of EPTB is about 15-20% of all TB cases. Global annual incidence of EPTB has been increasing due to changing TB control practices, spread of HIV and high population growth. Burden of EPTB remained high as 10-34% among HIV negative

patients while among HIV positive cases it accounts for 50-70% in new TB cases.<sup>2</sup> World Health Organization (WHO) estimated that in 2007 about 34,000(15%) of newly reported TB cases were extrapulmonary.<sup>3</sup> The disease most often remained undiagnosed or even untreated due to prime difficulty with specimens that they yield very few bacilli and associated with low sensitivity of acid-fast bacilli smear and culture.

The diagnosis of EPTB remained a problem for clinicians however it may be diagnosed on the basis of biopsy or strong clinical evidences. Only 10% of the patients shows positive acid-fast staining while 35% to 65% of the patients show negative Zeihl-Neelsen (ZN) and culture results, only 12-70% of pleural fluid culture is positive while pleural fluid biopsy revealed granulomas in 50-70% of patients with pleural effusion.<sup>4</sup> Varieties of tests are used for the diagnosis of EPTB like tuberculin skin test or interferon-gamma assay but do not show accurate results.<sup>5</sup> Moreover routine histology or cytology cannot differentiate between the disease caused by TB or non-TB mycobacterium, or chronic inflammatory conditions. There are some new techniques used for early detection of Mycobacterium tuberculosis among EPTB patients which include radiometric and non-radiometric assay together with improved molecular and diagnostic capacity but use of these techniques

is very low in resource limited settings thus remain an important public health problem.<sup>5</sup>

Pakistan is among highest TB and drug resistance TB burdened countries around the globe. According to Global TB report 2018, incidence of TB is 267/100,000 population while mortality rate of 27/100,000 is high as compared to previous report which presented mortality of 23/100,000 people.<sup>6,7</sup> Currently an incidence of EPTB is 14% globally however it is 24% in Eastern Mediterranean Region from where the country belongs.<sup>6</sup> Though a lot of focus has been given in diagnosis and treatment of pulmonary TB but EPTB remained under reported due to variety of infection sites involved and deficiency of definite diagnostic approaches. Present study was undertaken to observe variety of diagnostic techniques used for detection of EPTB, most common infection sites and treatment outcome among patients visiting tertiary care setting.

## Methodology

This descriptive study was undertaken in PHRC TB Research Centre in collaboration with Department of Pulmonology, King Edward Medical University/ Mayo Hospital Lahore during January 2016 to August 2017. After taking an informed consent from the patients of age 15 years and above, seeking treatment from outpatients were recruited in this study. Both male

Table 1: Type and diagnostic approach of Extra-pulmonary TB Cases (N=687)

Sr.No.	Type/Site of TB	Reported Cases N (%)	Diagnostic Approach Used - n (%)					
			Smear*/ Culture*	Histo/Cyto*	X-ray	Ultrasound	MRI#	CT^
1	Chronic Lymph Node	280 (40.7)	24 (8.57)	256 (91.4)	-	-	-	-
2	Pleura	143 (20.8)	22 (15.3)	82 (57.4)	15(10.5)	24 (16.8)	-	-
3	Abdomen	119 (17.3)	6 (5.04)	26 (21.8)	3 (2.5)	34 (28.6)	21 (17.6)	29 (24.4)
4	Brain & Spinal	61(8.9)	2 (3.27)	23 (37.7)	-	-	21 (34.4)	15 (24.5)
5	Bone	18 (2.6)	-	-	-	-	4 (22.2)	14 (77.8)
6	Chest Wall	13 (1.9)	-	13 (100)	-	-	-	-
7	Abscess	7 (1.01)	-	-	-	3 (42.8)	-	4 (57.2)
8	Miliary	7 (1.01)	-	-	7 (100)	-	-	-
9	Pus	7 (1.01)	7 (100)	-	-	-	-	-
10	Axillary	6 (0.9)	-	6 (100)	-	-	-	-
11	Others	(3.7) 26	4 (15.4)	13 (50.0)	-	9 (34.6)	-	-
12	Total	687 (100)	65 (9.5)	419 (60.9)	25 (3.6)	70 (10.1)	46 (6.7)	62 (9.0)

+Positive, \*Histopathology/Cytology, #Magnetic Resonance Imaging, ^Computed Tomography Scan

and female patients were included. A semi structured questionnaire was used to collect basic information, history, site of infection and treatment category etc. Patients were further followed up to the completion of treatment. No interference with treatment, diagnostic approaches or standard procedure was made.

Data entry and analysis was done by using SPSS version 20.0. Qualitative data variables like gender, type/ site of EPTB, treatment outcome and types of diagnostic techniques used were presented if frequency and percentage. Quantitative data was presented in mean $\pm$  standard deviation (SD).

## Results

A total of 2096 patients were registered to get anti tubercular treatment (ATT) under directly observed treatment short course (DOTS) in outpatients Department of Pulmonology Mayo Hospital Lahore. Patients categorized and registered as EPTB were 718(35.6%). Out of these 718 patients, 31(4.3%) could not be followed due to various reasons as some of them did not provide consent and others were transferred out therefore 687 patients were included in final analysis. Mean age of these patients remained 28.8 $\pm$ 14.7 and female gender was predominant including 428 (62.3%), while male were 259 (37.7%)

with male to female ratio of 1:1.65.

Chronic lymph node was the predominant type among EPTB cases comprising 280(40.7%) of total, followed by pleural TB (20.8%), abdominal TB (17.3%) and spinal TB (8.9%). Rest of the types including bone, chest wall, and abscess, miliary, axillary, vitreous and pericardial TB comprise minor values. Various diagnostic approaches were used to diagnose EPTB including AFB smear & culture (9.5%), histopathology or cytology (60.9%), X-ray (3.6%), ultrasound (10.1%), magnetic resonance imaging (MRI) 6.7% and computed tomography (CT) scan (9.0%). Diagnostic approaches used according to site of EPTB are presented in table 1.

Treatment compliance and outcome among EPTB patients is shown in Table II. Eighty five (12.4%) of EPTB patients were treated in category-II while others in category-I. Reasons to treat patients in category-II include treatment after default 15/85, relapse 52/85, and failure 8/85. Most of the patients showed excellent compliance 60.9% while few had no compliance (3.5%) which was categorized as defaulters later. Data showed that 82.5% of the patients were treatment completed and only 12.4% patients were declared as cured.

Table 2: Treatment outcome of Extra-pulmonary TB patients

Treatment Measures	Response	Cat-I (n=602)		Cat - II (n=85)		Total (N=687)	
		n	%	n	%	n	%
Treatment Compliance	Excellent	363	60.3	56	65.9	419	60.9
	Good	113	18.7	16	18.8	119	17.4
	Poor	104	17.3	11	12.9	109	15.9
	No Compliance	22	3.7	2	2.4	24	3.5
	Total	602	100	85	100	687	100
Treatment Outcome	Defaulters	22	3.7	2	2.4	24	3.5
	Failures	6	1.0	5	5.9	11	1.6
	Completed	503	83.5	64	75.3	567	82.5
	Cured	71	11.8	14	16.4	85	12.4
	Total	602	100	85	100	687	100

## Discussion

More than 35% of total registered EPTB cases in present study are high as compared to 24% reported by WHO and elaborated that the most of EPTB patients are clinically diagnosed and likely to be under reported.<sup>6</sup> Since various body organs may be involved in case of EPTB therefore it remained a great dilemma

to probe the diverse system. A great support in terms of diagnosis is needed to provide facilities for tests like histopathology/cytology, ultrasound, MRI, CT scan and X-ray for diagnosis of various types of EPTB as presented in current study. Although AFB smear facility is available at primary health care levels but various issues create hurdles which ultimately delay

the diagnosis. Major problems in diagnosing EPTB includes low yield of AFB, in respective specimens lead to low sensitivity of smear and other diagnostic tests.<sup>8</sup> On the other hand culture on Lowenstein Jensen medium is gold standard for diagnosis of tuberculosis but facility is not readily available at primary care level moreover takes 4-8 weeks to provide results.

Gene Xpert MTB Rif Assay has contributed to improve the sensitivity and provide early diagnosis and reports rifampicin sensitivity also but different EPTB specimens like tissues/ biopsies are not processed on it. Similarly sensitivity of < 50% among fluids has been reported by using Gene Xpert in a meta-analysis.<sup>9</sup> The next generation of Gene Xpert with Ultra cartridge is showing significant performance as compared to current cartridges and WHO is evaluating this ultra-cartridge for diagnosis of EPTB and expects to lay down guide lines in upcoming report of 2019.<sup>6</sup> Contrary to AFB smear, culture and GeneXpert present study observe the reliance of other diagnostic approaches to manage the cases.

Lymph node TB was the most common site of infection in this study and basis of its diagnosis was dominated (91.4%) by histopathological observation of granulomatous reaction and only 8.57% specimens diagnosed by AFB smear or culture. Characteristics of granuloma are composed of chronic inflammation induced by monocytes as a result of immune response which later fuse to show giant cell.<sup>10</sup> A recent study recommended histopathology/ cytology as a best tool in diagnosis of lymph node TB to start ATT.<sup>10</sup> A study conducted in a private hospital of Karachi reported around 69% lymph node TB is very high as compared to our present study but in agreement regarding most common type among EPTB.<sup>11</sup>

Pleural TB remained the second most common (20.8%) was the most common type of disease in present study and in accordance with another study conducted in India<sup>12</sup> but not comparable with former study.<sup>11</sup> Variety of approaches being used for its diagnosis mainly cytology which rely on lymphocytes count as is the case in present study. Around 57% patients were diagnosed on this basis with clinical correlation. Microbiology of pleural fluids remained helpful in diagnosis of around 15% patients is comparable with study that reported smear positivity of 10% and culture positivity of 20%.<sup>12</sup> X-ray and ultrasound are also helpful in diagnosis but clinical association and history of contact or previous treatment are also kept in consideration. Likewise cytology, ultrasound, MRI and CT scan remained important in diagnosis of abdominal TB and results are concordant to previous study from similar

settings.<sup>13</sup>

Excellent treatment compliance (60.9%) was observed in most of the study subjects followed by good (17.4), poor (15.9%) and no compliance (3.5%). The patients with no compliance were denoted as defaulters while 82.5% patients successfully completed their treatment while 12.4% were declared as cured by clinicians. The results are in agreement with previous studies.<sup>10,13</sup> Criteria for a cured pulmonary TB patient has been defined as to have smear or culture negative at the end treatment however diagnostic criteria of pulmonary TB is also based on smear and culture results but this generalization could not be applied on EPTB.

In conclusion EPTB is high and important public health problem in Pakistan. Chronic lymph node TB remained predominant followed by pleural and abdominal TB in present study. There are no guidelines available for definite diagnosis of verity of EPTB nationwide therefore multivariate approaches was used for its diagnosis based upon the site of infection. A good compliance and treatment outcome was observed among patients. A high number of patients fall in 'treatment complete' clause due to difficulty in acquiring complicated diagnostics and non-availability of proper strategies. Further research is needed in this regard to implement at least on tertiary care level.

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