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**Original Research**

# Effectiveness of LPA test with microscopy and culture method among pulmonary and extra pulmonary cases: A Comparative Study

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**Abstract**
**Aim**: To compare the effectiveness of LPA test with microscopy and culture method among pulmonary and extra pulmonary cases.
**Material and Methods**: The prospective study was conducted over a period of one year (February 2017 to January 2018) in the Department of Microbiology, Dayanand Medical College and Hospital. A total of 369 samples were received from 347 clinically suspected patients of tuberculosis in Department of Microbiology, DMCH. All the samples were processed and subjected to ZN staining. Smear-positive and negative samples were tested with Line probe assay and were inoculated on Lowenstein –Jensen media (conventional culture).
**Results**: Maximum positivity was revealed by line probe assay followed by direct microscopy in pulmonary cases. In extra pulmonary cases; maximum positivity was revealed by line probe assay followed by Conventional Culture (LJ). Out of 80 patients, Rapid culture (MGIT) was positive in 14 patients, Line probe assay was positive in 19 and 9 cases were positive by Direct microscopy and conventional culture (LJ).
**Conclusion**: LPA along with direct microscopy is a good screening method for early diagnosis and detection of drug resistance as it saves time and give results in 4 to 8 hours but are not a complete replacement for conventional culture which is still a gold standard.
**Keywords**: LPA, Microscopy, Culture, Pulmonary TB, Extra Pulmonary TB



**Introduction**:

Tuberculosis (TB) is a major public health disease caused by Mycobacterium tuberculosis (MTB), and has co-evolved with humans for many thousands of years or perhaps for several million years.[1] It primarily affects the lungs. It can also affect intestine, meninges, bones, joints, lymph glands, skin and other tissues of the body. The disease also affects animals like cattles and is known as, "Bovine tuberculosis" which may sometimes be communicated to man.[2]

TB transmission occurs through droplet nuclei containing MTB, which are expelled by smear-positive pulmonary TB patients when coughing and sneezing, and remain suspended in the air. Inhalation of such aerosols may lead to infection. MTB is most commonly transmitted through droplet nuclei (<10μm in diameter) from a patient with infectious pulmonary TB reaching terminal air passages when inhaled.[3] From this point, the progression of the disease can have several outcomes, determined largely by the response of the host immune system The efficacy of this response is affected by intrinsic factors such as the genetics of the immune system as well as extrinsic factors, e.g., insults to the immune system and the nutritional and physiological state of the host.[4] Clinical illness directly following infection is classified as primary TB and is common among children upto 4 years of age. The lesion of the primary

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disease is usually peripheral and accompanied by hilar or paratracheal lymphadenopathy which heals spontaneously as a small calcified nodule (Ghon lesion).[3]

Although it may progress causing meningitis or disseminated TB, especially in very young or immunosuppressed individuals, primary TB typically develops and spreads as caseating granulomas to regional lymph nodes and systemically for only a few weeks before regressing as immunity develops.[5-6]

Post primary, also known as adult type or secondary, tuberculosis, in contrast, occurs in people who have developed immunity to primary tuberculosis.[7-8] Overall, it is estimated that approximately 10% of persons infected in their youth develop TB, the risk is greatly increased in HIV infected persons.

Extra pulmonary tuberculosis (EPTB) describes the various conditions caused by Mycobacterium tuberculosis infection of organs or tissues outside the lungs. There are many forms of EPTB, affecting every organ system in the body. Some forms, such as TB meningitis and TB pericarditis, are life-threatening, while others such as pleural TB and spinal TB can cause significant ill-health and lasting disability. The burden of EPTB is high ranging from 15-20 per cent of all TB cases in HIV-negative patients, while in HIV-positive people, it accounts for 40-50 per cent of new TB cases. The estimated incidence of TB in India was 2.1 million cases in 2013, 16 per cent of which were new EPTB cases, equating to 336,000 people with EPTB.[9] The proportional rise in EPTB cases has been associated with the human immunodeficiency virus (HIV)/AIDS epidemic because there is increased susceptibility for reactivation and dissemination of tuberculosis in these patients.[10]

Several commercial systems using various technologies for the detection and identification of Mycobacterium spp. are in routine use, including DNA hybridization-based Accu Probe M. tuberculosis complex (MTBC) assay based on species-specific DNA probes, the INNO-LiPA MYCOBACTERIA Line Probe assay based on the nucleotide differences in the 16S-23S rRNA spacer region, GenoType Mycobacterium based on DNA hybridization technology on nitrocellulose strips, the Cobas Amplicor PCR system and the GEN-PROBE AMPLIFIED M. tuberculosis Direct (MTD) Test based on transcription-mediated amplification and the hybridization protection assay to qualitatively detect M. tuberculosis ribosomal ribonucleic acid.[11-12]

Line probe assays are test that use PCR and reverse hybridization methods for the rapid detection of mutations associated with drug resistance. LPA are designed to identify MTBC and simultaneously detect mutations associated with drug resistance. India has a high burden of multidrug-resistant tuberculosis (MDR-TB). The annual status report of TB India, 2014, mentioned that in 2012, the MDRTB amongst notified new pulmonary TB patients was 2.2 per cent, whereas amongst notified re-treatment pulmonary TB patients, it was 15 per cent Given the global situation of MDR-TB and an urgent need for detection of drug resistance amongst TB patients, LPA was introduced.[13]

TB is a social stigma and failure of adherence to treatment which includes both retreatment defaulters and new defaulters is associated as one of the factors which is responsible for the drug resistant TB cases. Hence, the present study was intended to the compare the effectiveness of LPA test (Geno Type MTBDR plus VER 2.0 assay) with microscopy and culture method among pulmonary and extra pulmonary cases in DMCH, Ludhiana.

**Material and Methods**:

The prospective study was conducted over a period of one year (February 2017 to January 2018) in the Department of Microbiology, Dayanand Medical College and Hospital. A total of 369 samples were received from 347 clinically suspected patients of tuberculosis in Department of Microbiology, DMCH. All the samples were processed and subjected to ZN staining. Smear-positive and negative samples were tested with Line probe assay and were inoculated on Lowenstein –Jensen media (conventional culture).

**Inclusion Criteria:** All pulmonary (sputum, pleural fluid, BAL, ET and others) and extra-pulmonary samples (CSF, tissue, pus, lymph node aspirate, ascitic fluid and others) were received from patients admitted in various wards and intensive care units in Department of Microbiology, Dayanand Medical College and Hospital, Ludhiana.

**Exclusion Criteria:** Blood and urine samples were not recommended to be processed using Line probe assay.

**Data collection:** The following data was collected from all the patients: name, age, sex, MRD number, specimen and lab number, clinical history, Hemoglobin (Hb), Total Leukocyte Count (TLC), Differential Leukocyte Count (DLC), ESR (Erythrocyte Sedimentation Rate), Mantoux test and Chest X-Ray findings.

**COLLECTION OF SPECIMEN:**

**Sputum:** Sputum was collected early in the morning before the patient had eaten or taken medication. 3-5 ml of sputum sample was collected in a clean, leak proof, disposable, wide-mouthed container.

**Endotracheal (ET) secretions:** The ET secretion was collected using a 22-inch Ramson's 12 F suction catheter with a mucus extractor which was gently introduced through the endotracheal tube for a distance of approximately 25–26 cm. Gentle aspiration was then performed without instilling saline and the catheter was withdrawn from the endotracheal tube. After the catheter was withdrawn, 2 ml of sterile

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0.9% normal saline was injected into it with a sterile syringe to flush the exudates into a sterile container for collection.

**Bronchoalveolar Lavage (BAL):** It required careful wedging of the tip of bronchoscope into an airway lumen isolating that airway from the rest of the central airway. Infusion of at least 120ml of physiological saline in several (3 to 6) aliquots was required for adequate sampling of pulmonary segment. The aspirate was then collected in a sterile, robust and leak proof container.

**EXTRA-PULMONARY SPECIMENS**

**Body fluids** like cerebrospinal fluid (CSF), pleural fluid, synovial fluid and ascitic fluid were collected taking all aseptic precautions in a sterile container.

**Pus:** Pus and discharge from wounds were collected in sterile container using cotton tipped swabs/ syringes. Tissue specimens were collected without preservatives or fixatives.

**TRANSPORTATION:** The samples were transported immediately to the microbiology laboratory for further processing. The samples were processed in the microbiology laboratory and all the processing was done in a biosafety cabinet.

**DIRECT EXAMINATION:** The smears were prepared directly from the sample and after concentration procedures and subjected to Ziehl-Neelsen (ZN). The smears stained by ZN method were examined under oil immersion of light microscope.

**CULTURE**: The processed samples were inoculated on the conventional Lowenstein-Jensen (L-J) media and in rapid Mycobacteria Growth Indicator Tube (MGIT) for isolation of mycobacteria.

**CONVENTIONAL METHOD**: Inoculation on Lowenstein-Jensen Media: 0.1 to 0.25ml of processed specimen was inoculated on L-J media and was incubated for 8 weeks.

**Examination of inoculated L-J media**: All culture bottles were examined daily for the first 7 days to detect rapid growers and to check for bacterial contamination. After that, the cultures were examined twice weekly till 8 weeks. Preliminary identification of mycobacteria was done on the basis of rate of growth, colony characteristics, ZN staining.

**INOCULATION IN MGIT**: MGIT PANTA was reconstituted with 15.0 ml MGIT growth supplement and mixed until completely dissolved. 0.8 ml of MGIT growth supplement/PANTA was added aseptically to each MGIT tube. Using a sterile pipette, up to 0.5 ml of a well-mixed concentrated specimen was added to the MGIT tube. Immediately the tube was recapped tightly and mixed by inverting the tube several times. The inoculated tubes were left at room temperature for 30 minutes. All inoculated MGIT were incubated at 37ºC ± 1ºC temperature for 6 weeks. Readings were recorded on daily basis using the BACTEC Micro MGIT. A reading of 14 and above was considered positive.

**RESULTS/REPORTING:**

**Positive:** In case of positive culture results were reported only when the MGIT tube was positive by the instrument and the smear made from the positive broth was also positive for AFB.

**Negative:** Negative cultures were reported after completing the incubation protocol of the instrument and visual observation of the negative tubes.

Data was collected and subjected to statistical analysis.

**Results**: Among 347 cases, pulmonary and extra pulmonary were 247 (71.2%) and 100 (28.8%) respectively as shown in table 1. Out of 347 patients, 83 pulmonary and 20 extra pulmonary cases were microbiologically confirmed. Out of 347 suspected cases of tuberculosis MGIT was performed on 80 samples and results were compared to other three modalities.

**Table 1: Distribution of pulmonary and extra pulmonary cases (n=347)**

| | No. of Patients | Percentage |
|---|---|---|
| Pulmonary | 247 | 71.2% |
| Extra-Pulmonary | 100 | 28.8% |
| **Total** | 347 | 100.0% |

The maximum positivity was seen in 46.4% of sputum samples. Maximum positivity was revealed by line probe assay followed by direct microscopy in pulmonary cases. In extra pulmonary cases; maximum positivity was revealed by line probe assay followed by Conventional Culture (LJ). In fluids (pericardial, peritoneal, drain, cyst) and sinonasal mucosa neither of the 3 modalities showed positive results (table 2).

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**Table 2: Sample wise positivity by different methods (n=347)**

| Sample | Number | Line probe assay (n=91) | | Direct microscopy (n=60) | | Conventional Culture (LJ) (n=56) | |
|---|---|---|---|---|---|---|---|
| **Pulmonary (n=247)** | | | | | | | |
| Sputum | 110 | 51 | 46.4% | 46 | 41.8% | 39 | 35.5% |
| Pleural fluid | 59 | 13 | 22.0% | 3 | 5.1% | 2 | 3.4% |
| Gastric aspirate | 41 | 3 | 7.3% | 1 | 2.4% | 1 | 2.4% |
| ET | 20 | 8 | 40.0% | 6 | 30.0% | 6 | 30.0% |
| BAL | 17 | 2 | 11.8% | 1 | 5.9% | 1 | 5.9% |
| **Extra Pulmonary (n=100)** | | | | | | | |
| CSF | 30 | 1 | 3.3% | 0 | 0.0% | 0 | 0.0% |
| Pus | 25 | 7 | 28.0% | 2 | 8.0% | 1 | 4.0% |
| Tissue | 20 | 4 | 20.0% | 1 | 5.0% | 5 | 25.0% |
| Lymph node aspirate | 4 | 1 | 25.0% | 0 | 0.0% | 1 | 25.0% |
| Lymph node biopsy | 2 | 1 | 50.0% | 0 | 0.0% | 0 | 0.0% |
| Fluids (Ascitic, Pericardial, Peritoneal, Drain, Cyst) | 18 | 0 | 0% | 0 | 0% | 0 | 0% |
| Sinonasal mucosa | 1 | 0 | 0% | 0 | 0% | 0 | 0% |

Out of 80 patients, Rapid culture (MGIT) was positive in 14 patients, Line probe assay was positive in 19 and 9 cases were positive by Direct microscopy and conventional culture (LJ) as shown in table 3.

**Table 3: Comparison of Mycobacterium detection by different method among various samples (n=80)**

| Sample | Number | Direct microscopy(n=9) | | Line probe assay (n=19) | | Conventional culture(L-J) (n=9) | | MGIT (n=14) | |
|---|---|---|---|---|---|---|---|---|---|
| **Pulmonary (n=48)** | | | | | | | | | |
| Sputum | 24 | 3 | 12.5% | 6 | 25.0% | 3 | 12.5% | 6 | 25.0% |
| ET | 10 | 4 | 40.0% | 5 | 50.0% | 4 | 40.0% | 4 | 40.0% |
| BAL | 6 | 1 | 16.7% | 1 | 16.7% | 1 | 16.7% | 1 | 16.7% |
| Pleural fluid | 8 | 1 | 12.5% | 2 | 25.0% | 0 | 0.0% | 1 | 12.5% |
| **Extra pulmonary(n=32)** | | | | | | | | | |
| Pus | 10 | 0 | 0.0% | 3 | 30.0% | 0 | 0.0% | 0 | 0.0% |
| CSF | 6 | 0 | 0.0% | 0 | 0.0% | 0 | 0.0% | 0 | 0.0% |
| Tissue | 9 | 0 | 0.0% | 2 | 22.2% | 1 | 11.1% | 1 | 11.1% |
| Ascitic fluid | 3 | 0 | 0.0% | 0 | 0.0% | 0 | 0.0% | 1 | 33.3% |
| Lymph node aspirate | 2 | 0 | 0.0% | 0 | 0.0% | 0 | 0.0% | 0 | 0.0% |
| Cyst fluid | 1 | 0 | 0.0% | 0 | 0.0% | 0 | 0.0% | 0 | 0.0% |
| Sinonasal mucosa | 1 | 0 | 0.0% | 0 | 0.0% | 0 | 0.0% | 0 | 0.0% |

**Discussion**:

TB referred to as white plaque or captain of death due to it continuous evolution over the time that resulted in the emergence and spread of multidrug-resistant strains which had hindered the achievement of future goals. New approaches to control TB worldwide are needed. New tools for diagnosis and new biomarkers are required to evaluate both pathogen and host key elements to evaluate the response to infection.[14] The present study showed comparative analysis of conventional methods for diagnosis of pulmonary and extra pulmonary cases with molecular methods.

Similar to a study from Turkey, our study showed 19.4% of EPTB cases. In the study among EPTB patients the females (51.7%) were more affected than males (48.2%) whereas in our study males (60%) were more commonly affected than females (40%). The most common sites involved were the lymph nodes and pleura, followed by the brain, psoas muscle and others whereas in current study the most common samples were tissue, pus, lymph node aspirate followed by others.[15]

The most sensitive means of detecting MTB is the culture of processed samples on solid egg-based media (Lowenstein–Jensen) with subsequent visualization of colonies. Use of selective liquid media and growth indicator systems increase both the sensitivity and speed of detection. Time to detection is shortest using liquid culture with continuous automated monitoring systems, approximately halving the time to detection compared with culture on solid media.[16]

Arslan et al [17] conducted a study in which direct microscopy and culture positivity was 11.33% and

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15.47% respectively where as in our study direct microscopy positivity was little higher 17.3% in comparison to culture positivity 16.1%. In smear positive cases 83% were found to be positive on L-J culture whereas in comparison to our study 76.6% were found to be positive on L-J culture.

In 2008, the WHO recommended the Line Probe Assay (LPA) as a rapid diagnostic tool to detect the presence of MTBC in the samples, but also reveals the resistance pattern against two first-line drugs, RIF and INH, with high accuracy. [18-20] A study from South Africa reported that sensitivity of LPA increases with burden of bacilli. The sensitivity of LPA in sputum smear negative was found to be 13.7%, smear scanty 46.2%, smear 1+ 69.1% followed by smear 2+ 86.3% and in smear 3+ 89.8% [21] whereas in our study the smear examination yielded the following bacillary load in line probe assay positive cases: 2 were graded as scanty, 19 as 1+, 16 as 2+, and 18 as 3+. Higher results were obtained from specimens with positive smear grading compared to those specimens with a scanty smear grading.

A study conducted by Jaishankar sharma and his colleagues strongly facilitates rapid detection of tuberculosis by comparing ZN, conventional culture and LPA positivity. The results showed 82% were positive by ZN staining, 80% were found to be culture positive and 95% were LPA positive which is concordant to our highest positivity of 26.2% in LPA, 17.3%of ZN staining followed by 16.1% of conventional culture.[22]

Diagnostic performance of Genotype MTBDRplus VER 2.0 LPA in direct smear positive sputum sample was highly sensitive and specific for early detection of MDR-TB using MGIT as a gold standard. A study was conducted by Binnit kumar et al showed the similar results in which LPA was able to diagnose MTBC in 38.2% of specimens. Sensitivity and specificity of the assay were 68.4% and 89.3% respectively, considering MGIT-960 culture as gold standard in smear negative TB.[23]

A similar study was conducted by Abyot maeza et al which evaluated the utility of latest version of LPA for the detection of MTB considering MGIT-960 culture as gold standard that showed both higher sensitivity (77.8%) and specificity (97.9%) for sputum smear negative patients[24] whereas in our study the sensitivity and specificity of Genotype MTBDR plus VER 2.0 LPA were 20.0% and 84.85% respectively hence the sensitivity of the assay should be improved for detection of MTB in direct smear negative cases.

In present study a total of 7(2.01%) samples which were grown in conventional culture but was found to be negative by LPA the reason could be NTM or the presence of inhibitors in the samples. Another study from India had reported 3.4% isolation of NTM from extra pulmonary samples.[25]

MTB culture is still the cornerstone on which definitive diagnosis of TB relies. Egg-based LJ media has been used for cultivation of Mycobacteria for several decades. Liquid media have been introduced to increase the diagnostic yield of mycobacteria. MGIT was introduced about a decade ago with the aim of increasing the sensitivity of culture.

The present study demonstrated that rapid culture (MGIT) provided better isolation rate of mycobacteria 14 (17.50%) from a variety of clinical samples compared to solid media 9 (11.25%). The obtained results are in agreement with those reported by Hanna et al, which showed that the BACTEC MGIT 960 system had a recovery rate higher than solid media.[26] Dongsi and Dunnc M. also found that the BACTEC MGIT 960 system consistently provided with better isolation rates of all Mycobacterium species from a variety of clinical specimens than the traditional L.J. slants.[27] Another study conducted in Spain had reported the sensitivity of MGIT to be 93% as compared to only 60% with L-J medium.[28]

Liquid cultures generally require a shorter incubation time than solid media for detection of M. tuberculosis.

**Conclusion**:

Direct microscopic examination is still the only available diagnostic tool in many resource-poor settings. The core problem is that it misses many cases of tuberculosis, especially the paucibacillary ones and has low sensitivity but due to its low cost and ability to detect highly infectious cases it still remains the most effective tool in diagnosing TB. Mycobacterial culture on conventional egg-based media has remained the gold standard for diagnosis. Due to the relatively long incubation period of mycobacteria as compared to other bacteria, there has always been delay in diagnosing. To overcome this problem introduction of liquid culture media are being increasingly used as they shorten the incubation period for diagnosing TB by 3 to 4 weeks and yielding better results.

LPA can be applied directly to clinical specimens (without the need for isolating the strain first on solid or liquid culture). It can also be used on specimens that are not suitable for growth–based assays, such as specimens containing non-viable bacteria (killed by heat or chemical inactivation during drug therapy), specimens highly contaminated with nonmycobacterial flora, or specimens with mixed TB and NTM.

However, LPA along with direct microscopy is a good screening method for early diagnosis and detection of drug resistance as it saves time and give results in 4 to 8 hours but are not a complete replacement for conventional culture which is still a gold standard.

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