# Overview of diagnosis procedures of tuberculosis

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## Abstract:

Pulmonary tuberculosis (TB) continues to be a important public health problem, which reinforced the need for rapid diagnostic improvements and new modalities to detect TB and drug-resistant TB, as well as to improve TB control. Standard guidelines and recent advances for diagnosing pulmonary TB are summarized in this review. PubMed and Embase were searched for eligible studies that discussing the diagnosis and management approaches of tuberculosis up to November 2017. Despite continuous effort in monitoring and therapy of tuberculosis, the disease stays a significant public health issue. Rapid diagnosis and proper therapies become the first priorities in controlling the growing epidemics. The bedside decision on the initiation of anti-tuberculous drug treatment are based upon epidemiologic, clinical, radiographic, and/or histological findings, which can usually be sustained by a fast microbiologic test, commonly a favorable acid-fast bacilli (AFB) smear outcome.



## Introduction:

Tuberculosis (TB) remains the leading cause of fatality from a curable infectious illness, in spite of the availability of short-course treatment that can be both cost-effective and effective. Clinical management of situations in establishing nations is hampered by the lack of a simple and efficient diagnostic test [1].

Active tuberculosis (TB) is diagnosed by discovering Mycobacterium tuberculosis complex bacilli in samplings from the breathing tract (pulmonary TB) or in samplings from other physical sites (extra pulmonary TB). Although numerous brand-new (molecular) diagnostic methods have been established, acid rapid bacilli (AFB) smear microscopy and culture on Lowenstein-Jensen medium are still the "gold requirements" for the diagnosis of energetic TB and, particularly in lowresource nations, the only techniques readily available for confirming TB in patients with a scientific presumption of active disease. AFB smear microscopy is rapid and cost-effective and hence is an extremely beneficial method to identify very contagious patients. Culture is used to detect instances with low mycobacterial loads and is also requested in cases in jeopardy of drug-resistant TB for drug sensitivity testing, or in situations where illness because of another member of the Mycobacterium genus is suspected. AFB smear microscopy and society could also be utilized to keep track of the performance of treatment and can aid to determine when a patient is much less most likely to be infectious. Two manuals are suggested for the laboratory diagnosis of TB [2], [3].



Appropriate medical diagnosis of TB is needed to enhance treatment, lower transmission, and control advancement of medicine resistance. In patients with energetic pulmonary TB, only an approximated 45% of infections are discovered by sputum microscopy. This test, first developed in the 1880s and essentially unmodified today, has the advantage of being simple, yet is interfered with by really reduced sensitivity: it might just identify fifty percent of all instances with active infection. It is additionally extremely depending on the ability of the service technician, and a solitary service technician could only refine a fairly tiny number of slides daily [3].

Pulmonary tuberculosis (TB) continues to be a important public health problem, which reinforced the need for rapid diagnostic improvements and new modalities to detect TB and drug-resistant TB, as well as to improve TB control. Standard guidelines and recent advances for diagnosing pulmonary TB are summarized in this review.

## Methodology:

PubMed and Embase were searched for eligible studies that discussing the diagnosis and management approaches of tuberculosis up to November 2017, search strategy used MeSH／terms and free text words, and included sub-searches related to the index test, target condition, study population and publication type. A methodological filter for the identification of relevant studies was added to increase the specificity of the search. Reference lists of all retrieved concerned studies were checked for additional relevant studies.



## Discussion:

- **DIAGNOSIS**

There specify epidemiological aspects that provide added difficulties to TB diagnosis. HIV infection is believed to be a significant contributor to the increase in TB occurrence across the globe [2].An estimated 9% of grownups globally with newly diagnosed TB are HIV positive. HIV co-infection with TB offers obstacles to reliable diagnosis of TB and diagnosis could

additionally be harder in children. The rapid increase of drug-resistant (DR) TB has further made complex TB diagnosis [6]. Examinations that determine medication susceptibility are important to monitor the spread of resistant TB stress, and make sure that patients are offered efficient therapy. New diagnostic tests that are easy and durable enough to be used in the area, exact enough to diagnose all contaminated individuals, and able to recognize drug resistance are frantically needed, and stand for a necessary enhance to new medicine advancement initiatives and to effective control and therapy programs.

An individual who is suspected of having TB disease requires a complete medical evaluation, including the following [4]:

1. Medical history, including exposure, symptoms, previous treatment for TB, and risk factors.

2. Human immunodeficiency virus (HIV) screening.

3. Physical examination.

4. Tuberculin skin test (TST) or interferon gamma release assay (IGRA).

5. Chest radiography.

6. Bacteriologic examination.



- **MEDICAL HISTORY**

Clinicians need to ask concerning the patient's history of TB direct exposure, infection, or condition. It is also crucial to think about group elements, (e.g., native land, age, ethnic or racial team, occupation) that might enhance the patient's danger for direct exposure to TB or to drugresistant TB. Likewise, clinicians must identify whether the patient has medical conditions,

especially HIV infection, that enhances the threat of unrealized TB infection progressing to TB condition [5].

- **HUMAN IMMUNODEFICIENCY VIRUS SCREENING**

Voluntary therapy and testing for HIV is recommended for all patients with TB. HIV therapy and screening has likewise been suggested for get in touches with of individuals with TB [6].The Centers for Disease Control and Prevention (CDC) advises the following:

- Routine HIV screening for all patients ages 13-64 seeking healthcare for any type of reason, without regard to any patient's known dangers for HIV infection.

- Annual HIV screening of patients understood to be at high danger [7].

- **PHYSICAL EXAMINATION**



A physical examination could provide beneficial info about the patient's overall condition and other variables that might impact exactly how TB is treated, such as HIV infection or other diseases.

- **TEST FOR TB INFECTION**

The Mantoux tuberculin skin test (TST) or the unique TB blood examination can be utilized to evaluate for M. tuberculosis infection. Extra examinations are needed to verify TB condition. The Mantoux tuberculin skin examination is executed by infusing a small quantity of fluid called tuberculin right into the skin in the reduced part of the arm. The examination reads within 48 to 72 h by a trained healthcare worker, who seeks a reaction (induration) on the arm.The special TB blood examination measures the patient's immune system response to M. tuberculosis.

- **CHEST RADIOGRAPH**

A posterior-anterior chest radiograph is used to identify upper body problems [19]. Lesions could appear anywhere in the lungs and could differ in size, shape, density, and cavitation. These problems might recommend TB, but can not be made use to definitively detect TB. However, a breast radiograph might be made use of to dismiss the possibility of pulmonary TB in an individual who has had a favorable response to a TST or special TB blood test and no symptoms of disease [8].

- **DIAGNOSTIC MICROBIOLOGY**

The presence of acid-fast-bacilli (AFB) on a sputum smear or various other specimen frequently suggests TB condition. Acid-fast microscopy is easy and fast, but it does not verify a diagnosis of TB due to the fact that some acid-fast-bacilli are not M. tuberculosis. Therefore, a society is done on all initial examples to validate the diagnosis. (However, a favorable culture is not always needed to begin or proceed treatment for TB). A positive culture for M. tuberculosis verifies the medical diagnosis of TB illness. Culture assessments should be completed on all samplings, no matter of AFB smear results [11].Laboratories must report positive outcomes on smears and cultures within 24 h by telephone or fax to the primary health care provider and to the state or neighborhood TB control program, as needed by law.



- **MATERIALS AND METHODS**

### Specimens

The successful isolation of the pathogen requires that the very best specimen be correctly gathered, promptly moved and meticulously processed. Various kinds of scientific specimens could be acquired for the microbiological diagnosis. If pulmonary TB is suspected, specimens originating from the respiratory system needs to be accumulated, i.e., sputum, generated sputum,

broncho alveolar lavage or a lung biopsy. For the diagnosis of pulmonary TB, 3 first-morning sputum specimens (not saliva) gotten after a deep, productive cough on non-consecutive days are typically recommended. Numerous researches have revealed, however, that the value of the 3rd sputum is negligible for the diagnosis of TB, as virtually all situations are recognized from the initial and/or the second specimen [12].Samplings to be gathered for the medical diagnosis of extrapulmonary condition depend on the site of the condition. One of the most typical samplings obtained in the laboratory are biopsies, aspirates, pus, urine, and normally sterile body fluids, consisting of cerebrospinal fluid, synovial, pleural, pericardial, and peritoneal liquid. Feces can be collected when intestinal tract TB is presumed and likewise when it comes to thought Mycobacterium avium infection in AIDS patients.

## AFB Smear



AFB smear microscopy plays a crucial function in the early diagnosis of mycobacterial infections since most mycobacteria expand slowly and society results appear just after weeks of incubation (Table 1). Additionally, AFB smear microscopy is typically the only offered diagnostic approach in establishing nations. Smear staining is based upon the high lipid content of the cell wall of mycobacteria that makes them resistant to decolorization by acid-alcohol after the primary staining [13].To determine that a medical specimen contains AFB, the specimen is spread out into a microscope slide, heat-fixed, tarnished with a primary staining, decolorized with acid-alcohol solution and counterstained with a different dye in order to acquire better differentiation between the bacterium and the history. The slide is observed under the microscope for the discovery of AFB.Several approaches could be utilized for identifying the acid-fast nature of an organism.

**Table 1:** Showing the Count of Mycobacterium Bacilli in per Fields of 100x

| Count on Ziehl-Neelsen/Kinyoun stain (1000x) | Report |
|---|---|
| 0 | Non AFB observed |
| 1–9/100 fields | Exact count |
| 10–99/100 fields | 1+ |
| 1–10/field | 2+ |
| > 10/field | 3+ |

Diagnostic methods in detection of Mycobacterium Tuberculosis are as follows:

1. Culture based methods

2. Non culture based methods.

## Culture Based Methods

Culture of Mycobacterium tuberculosis remains the gold criterion for both medical diagnosis and medicine sensitivity testing. This area examines culture examinations presently being used, and recently developed strategies. Conventional culture techniques using Lowenstein-Jensen (LJ) or 7H11 medium, while cheap and easy, have the significant drawback of being extremely slow. LJ cultures take 20-56 days for diagnosis and 4 to 6 weeks after preliminary society for medicine sensitivity testing [14].7H11 medium slightly speeds up the process, however requires antibiotics in the medium to stop contamination and a CO2 incubator. Diagnosis with 7H11 tool takes 17-21 days, Daylight Saving Time (DST) details is readily available three to 6 weeks later. Some more rapid society methods have been established and are commercially readily available, a lot of which are difficult to apply in the field because of the intricacy of the method or the required devices. There are likewise some emerging simplified society strategies that can minimize time to medical diagnosis or DST that seem better for use in resource-limited setups.

The sensitivity of culture is limited by the requirement to have bacilli present in the sample to be cultured. HIV positive patients and children have difficulty in creating sputum and sputum society will certainly not find extrapulmonary (EP) kinds of TB. EP TB is typical in HIV positive patients and is rapidly deadly [15].Even in patients with energetic pulmonary TB, the bacilli may

be secured in lung dental caries or otherwise existing in a certain sputum sample, or may be shed in the decontamination therapy required to refine spit for mycobacterial culture. All these factors restrict the effectiveness of the strategy.

## New Rapid Commercial Methods for Diagnosis and DST

A variety of commercial systems are readily available for culture and DST, a few of which might have small advantages in certain setups. However, none of the examinations are quickly versatile to the truths of field tasks, offered the difficulties in establishing and running society laboratories.

## Phage-based Tests

Phage-based tests require minimal culture facilities and promise rapid results (~ 2 days). However, MSF area assessments revealed that it is really tough to apply in non-culture facilities in the area, even in fairly wellsupported city settings [16] Dedicated locations are needed, cautious control of access to the rooms is required to lower contamination, and even relatively basic demands, like a steady power supply and an operating biosafety hood, are extremely difficult and typically tremendously costly to ensure. Metanalyses contrasting phage based tests to society in area settings have revealed that in many cases they disappear insightful that smear microscopy.



## Non-Culture Methods

A variety of strategies to detect and report the visibility of M. Tuberculosis have been created. Serology (detection of antibodies) has not generated any kind of reputable, useful examinations regardless of years of work. Detection of antigens is a much more encouraging strategy, as it discovers the existence of the organism and thus may have the ability to diagnose active infection. The use of nucleic acid amplification (NAA) tests in non-specialised labs is practically

challenging [18].These tests have been revealed to be extremely particular, however sensitive if starting from patient samples, low and very variable and is difficult to evaluate.These tests can likewise be used from primary culture. Although this improves the level of sensitivity, the strategy is after that really slow. Because of this, we have chosen to include NAA tests in the nonculture area of this report, in order to concentrate on the tests' use on straight scientific samples. Here we additionally check out some polymerase chain reaction (PCR) based methods which are being validated for usage on patient samples for fast discovery of rifampicin/isoniazid resistance. There are additionally some tests being established that detect immunological actions (interferon gamma assays). These tests are instead costly and challenging to carry out, and still require to be verified in endemic locations, and their interpretation is not clear.

## Strategies using Antibody Detection



In 2005, WHO/TDR did an examination of readily available fast diagnostic tests (RDTs). Twenty-seven makers were invited to send their products for assessment, however of the 19 who concurred, just 6 provided info on the antigen utilized. All examinations identify antibodies in serum [17].Test examples came from the TDR specimen bank. The WHO research located that TB fast analysis tests currently offered on the market differ widely in efficiency, with some items revealing a high lot-to-lot and readerto-reader irregularity. At much less compared to 80%, the specificity was poor in the majority of products when examined in TB suspected cases from endemic setups. Those tests with a better uniqueness (over 90%) had poor level of sensitivity, detecting less than 40% of TB patients. The examinations done also worse in HIV co-infected examples. The conclusion of the study was that none of the assays execute well enough also to replace microscopy [9].Based upon this and various other details, it appears that antibody discovery is not likely to be an excellent approach for the growth of a reliable diagnostic

examination for TB. It is crucial to note that the examinations named in the above table are only those that consented to get involved in the study: absence from the checklist does not indicate that the test functions. We located no convincing evidence sustaining the use of any existing antibody detection examinations [10].

## Conclusion:

Despite continuous effort in monitoring and therapy of tuberculosis, the disease stays a significant public health issue. Rapid diagnosis and proper therapies become the first priorities in controlling the growing epidemics. The bedside decision on the initiation of anti-tuberculous drug treatment are based upon epidemiologic, clinical, radiolographic, and/or histological findings, which can usually be sustained by a fast microbiologic test, commonly a favorable acid-fast bacilli (AFB) smear outcome. Nevertheless, AFB smear is positive in only half of patients with subsequently culture favorable for Mycobacterium tuberculosis. Although the sensitivity of the smear is improved by fluorescent staining, the test cannot compare tuberculous and nontuberculous mycobacteria. Diagnosis of Tuberculosis (TB) is primarily based on the culture approach and non-culture techniques. Molecular techniques are coming to be more advanced and confirmatory diagnostic procedure of TB. Current surveys also reveal that drug-resistant tuberculosis is still common and alarmingly high in numerous countries.



## Reference:

1. World Health Organization. The World Health Report 2003: Changing History. Geneva, Switzerland, 2004.

2. PT Kent, GP Kubica. Public Health Mycobacteriology: A Guide for the Level III Laboratory. US Department of Health and Human Services, 1985. CDC, Atlanta, Georgia.
3. Master, R.N. Section Editor. "Mycobacteriology". Clinical Microbiology Procedures Handbook, 1: ASM, Washington D.C. 1992.
4. In the WAC, see Chapter 246-101 (Notifiable Conditions) in the Title 246 (Department of Health) at http://apps.leg.wa.gov/wac/default.aspx?ci te=246-101.
5. American Thoracic Society (ATS) and CDC. Diagnostic standards and classification of tuberculosis in adults and children. Am. J. Respir. Crit. Care. Med. 2000; 161: http://ajrccm.atsjournals.org/cgi/content/fu ll/161/4/1376
6. ATS, CDC, IDSA. Controlling Tuberculosis in the United States: Recommendations from the American Thoracic Society, CDC, and the Infectious Diseases Society of America. MMWR 2005; 54(No. RR-12): 51p.
7. CDC. Revised Recommendations for HIV Testing of Adults, Adolescents, and Pregnant Women in Health-Care Settings. MMWR 2006; 55(No. RR-14): 1–17p.
8. CDC. Medical Evaluation. In: Chapter 5: diagnosis of TB. Core Curriculum on Tuberculosis (2000) [Division of Tuberculosis Elimination Web site]. Updated November 2001. Available at: http://www.cdc.gov/tb/education/corecurr/ index.htm. Accessed March 11, 2011.
9. J.Cunningham, Presented at 36th Union World Conference on Lung Health of the International Union Against Tuberculosis and Lung Disease, Paris 2005.
10. ATS, CDC, and Infectious Diseases Society of America. Treatment of Tuberculosis. MMWR 2003; 52 (No. RR11).http://www.cdc.gov/mmwr/PDF/rr/rr5 211.pdf.
11. Clinical and Laboratory Standards Institute. 2008. Laboratory detection and identification of mycobacteria; approved guideline—1st edition. CLSI document M48-A. Clinical and Laboratory Standards Institute, Wayne, PA.
12. Pfyffer G. 2015. Mycobacterium: general characteristics, laboratory detection, and staining procedures, p 536–569. In Jorgensen J, Pfaller M, Carroll K, Funke G, Landry M, Richter S, Warnock D (ed), Manual of Clinical Microbiology, 11th ed. ASM Press, Washington, DC.
13. Tran S, Renschler J, Le H, Dang H, Dao T, Pham A, Nguyen L, Nguyen HV, Thi Thu Nguyen T, Ngoc Le S, Fox A, Caws M, Thi Quynh Nguyen N, Horby P, Wertheim H. 2013. Diagnostic accuracy of microscopic observation drug susceptibility (MODS) assay for pediatric tuberculosis in Hanoi, Vietnam. PLoS One 8:e72100. 10.1371/journal.pone.0072100.
14. Clinical and Laboratory Standards Institute. 2011. Susceptibility testing of mycobacteria, Nocardiae, and other aerobic actinomycetes; approved standard—2nd ed. CLSI document M24-A2. Clinical and Laboratory Standards Institute, Wayne, PA.
15. Crampin AC, Floyd S, Mwaungulu F, Black G, Ndhlovu R, Mwaiyeghele E, et al. Comparison of two versus three smears in identifying culture-positive tuberculosis patients in a rural African setting with high HIV prevalence. Int J Tuberc Lung Dis 2001;5: 994-9.

16. Wang M, Fitzgerald JM, Richardson K, Marra CA, Cook VJ, Hajek J, et al. Is the delay in diagnosis of pulmonary tuberculosis related to exposure to fluoroquinolones or any antibiotic? Int J Tuberc Lung Dis. 2011;15:1062–1068.
17. National Institute for Health and Clinical Excellence. Tuberculosis: clinical diagnosis and management of tuberculosis, and measures for its prevention and control. London: National Institute for Health and Clinical Excellence; 2011.
18. Wilson ML. Recent advances in the laboratory detection of Mycobacterium tuberculosis complex and drug resistance. Clin Infect Dis. 2011;52:1350–1355.
19. Lee KS, Song KS, Lim TH, Kim PN, Kim IY, Lee BH. Adult-onset pulmonary tuberculosis: findings on chest radiographs and CT scans. AJR Am J Roentgenol. 1993;160:753–758.