CODEN [USA]: IAJPBB ISSN : 2349-7750

INDO AMERICAN JOURNAL OF
PHARMACEUTICAL SCIENCES

SJIF Impact Factor: 7.187

https://doi.org/10.5281/zenodo.7276936

Available online at: http://www.iajps.com *Review Article*

AN OVERVIEW OF LABORATORY AND RADIOLOGICAL DIAGNOSTIC OF TUBERCULOSIS

Soaad Hamdi Allugmani, Wael Ismail Mandili, Kholood Saleh Kably, Mohammad Abdullah Basrdah, Abeer Saleh Kabli, Bothainah Yousef Mohammad Abdullah, Manal Bakor Mohamed, Abrar Yousef Ghulam, Abdulaziz Amin Saber Alandijani

Article Received: September 2022 **Accepted:** September 2022 **Published: October** 2022

Abstract:

Diagnosis of tuberculosis (TB) is difficult, since symptoms are often very unspecific or lacking. However active, prompt and accurate diagnosis is the key element in the public health response to tuberculosis and the cornerstone of tuberculosis control. We conducted narrative review through the litruture, for all studies that were published up to the beginning of 2021. Different diagnostic procedures are required for an accurate diagnosis of tuberculosis. Although chest radiography is a significant tool in identifying tuberculosis, radiography alone cannot establish tuberculosis diagnosis. CT scanning is utilized to identify TB from other diseases in individuals who do not have abnormal chest radiography but are clinically suspected of having active TB. The radiological appearance of patients is mostly determined by their immunological status, and caves and widespread disease foci are frequently found. Microscopic detection of acid-fast mycobacteria from any fluid (particularly sputum) as well as isolation and characterisation of mycobacteria in culture are examples of laboratory diagnostic procedures. The pathogens can then be classified based on the morphology of their colonies, growth patterns, and biochemical properties.

Corresponding author:
Soaad Hamdi Allugmani,

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Please cite this article in *Soaad Hamdi Allugmani et al,* ***An Overview Of Laboratory And Radiological Diagnostic Of Tuberculosis., Indo Am. J. P. Sci, 2022; 09(10).***

INTRODUCTION:

Tuberculosis (TB) is caused by Mycobacterium tuberculosis complex mycobacterial species. Although M tuberculosis is responsible for the vast majority of cases, other species, such as Mycobacterium bovis, Mycobacterium africanum, Mycobacterium microti, and Mycobacterium canettii, can produce identical disease [1]. When a person with active tuberculosis coughs, sneezes, or speaks, droplets 1-5 m in diameter can remain suspended in the air for several hours, transmitting mycobacteria [1]. Not everyone who is exposed to TB becomes afflicted. Globally, 10.4 million TB incident cases were reported in 2015, with an estimated incidence of [2]. According to the World Health Organization's (WHO) Global TB Report 2016, TB killed 1.4 million individuals in 2015 [2]. The 30 countries with the highest TB burden accounted for 87% of all estimated incident cases worldwide [2]. Imaging is crucial in the first assessment of individuals suspected of having active TB. (**Figure 1**) [3] depicts a strategy for evaluating such a patient. If the chest radiograph is negative and the patient is HIV negative, there may be no need for additional testing. If the chest radiograph reveals active tuberculosis or the patient is HIV positive, laboratory testing for active tuberculosis should be conducted [3].

Sputum Smear Microscopy is the most commonly used imaging technique for diagnosing tuberculosis (SSM). This is the most often used diagnostic technique, with about 77.6 million SSM tests performed globally each year [4]. Despite being the most often used test, it has the lowest sensitivity (about 50%) of any TB test now available. To our knowledge, micro and nanofluidics have not yet been used to improve the way SSM is performed. However, the method has been utilized to improve tuberculosis diagnosis by automating microscopic imaging and immobilizing bacteria with cell-fixing chemicals rather than heat-fixation, as is commonly done in SSM. A 12-hour time-lapse series was created. Their work showed the feasibility of using real-time analysis and long-term culture of mycobacterium for phenotypic testing [5].

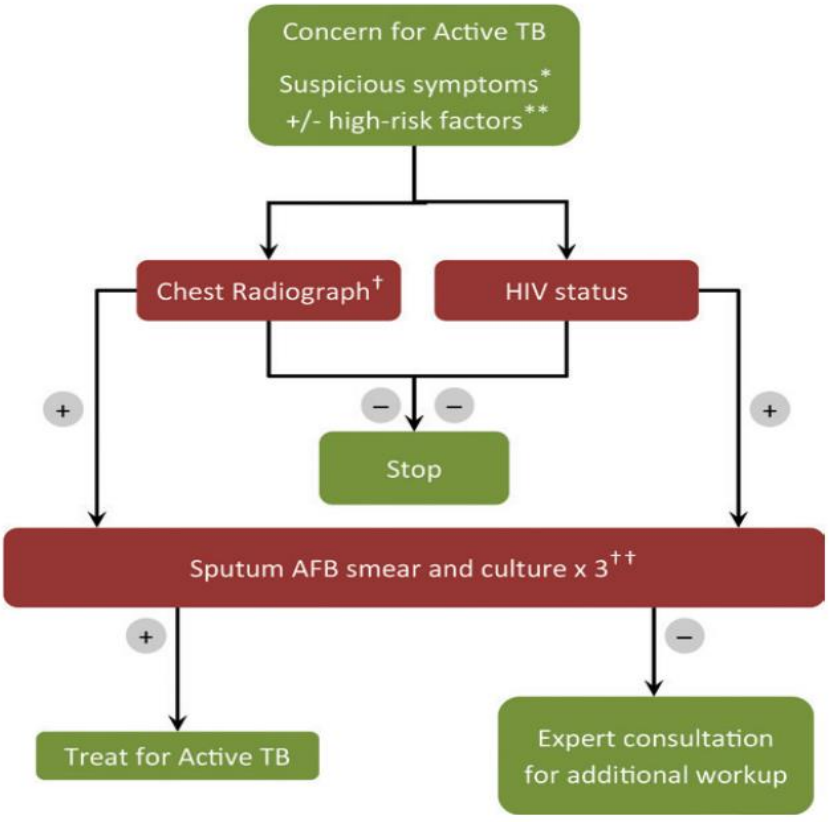

Figure 1. Diagram of an algorithm for the evaluation of patients who are suspected of having active tuberculosis (TB)

DISCUSSION:

Laboratory methods to diagnose TB:

Direct Tests:

Microscopy Because most mycobacteria grow slowly and culture data are only available after weeks of incubation, acid-fast bacilli (AFB) smear microscopy is useful in the early detection of mycobacterial infection. Furthermore, in developing countries, AFB smear microscopy is frequently the only available diagnostic approach. This procedure is quick, simple, and economical, and it may be conducted directly on clinical specimens without the use of a high-tech laboratory. It can identify at least 5000 to 10,000 bacilli per milliliter of sputum. Various investigations using microscopy to diagnose pulmonary tuberculosis have revealed sensitivities ranging from 20% to more than 80%. Thus, a strategy to improve the sensitivity of microscopy is urgently required. The sensitivity of smear microscopy has been increased by concentrating sputum specimens with or without chemical processing. According to a systematic review that summarized the findings of various published primary studies evaluating the various combinations of physical (centrifugation, sedimentation) and chemical methods (sodium hydroxide, N-acetyl-L-cysteine, bleach, ammonium sulfate, dithiothreitol), chemical processing followed by centrifugation offers increased sensitivity without sacrificing specificity when compared to direct microscopy [6].

Culture:

Traditionally, culture has been considered the gold standard, and good culture has been utilized to establish TB diagnosis. Although it has higher sensitivity than smear microscopy, it has a long turnaround time (TAT) of 4 to 8 weeks. Furthermore, drug susceptibility testing (DST) takes 2 to 3 weeks, adding to the delay in initiating adequate antitubercular medication. Broth-based liquid cultures have significant advantages over solid cultures in that they can detect as few as 10 to 103 live bacilli per milliliter of specimen, boosting case yield by 10%. A systematic review has reported higher sensitivity of BACTEC MGIT 960 than solid culture (88% vs 76%); the pooled use of both these culture systems further increased the detection yield to 92% [7].

Liquid culture was shown to be more positive than solid culture (7.5% vs 4.3%). The WHO suggested using liquid medium for culture and DST, emphasizing the necessity for quick diagnostic methods that aid in species identification. However, these liquid culture systems have limitations: (1) They are more susceptible to contamination by other nonmycobacterial organisms (8.6%) or nontuberculous mycobacteria (NTM); even in skilled laboratories, 5% to 7% of specimens fail to give results due to contamination [8]. (2) Cross-contamination across samples during culture inoculation is conceivable (4%), with bacilli being carried over from positive to negative specimens. According to a recent study, liquid culture techniques are more accurate and cost-effective than solid cultures for diagnosing tuberculosis in HIV-positive individuals in a resource-constrained situation [9]. Thus, for the efficient operation of a laboratory, thorough planning and systematic implementation of culture facilities should be considered, with a focus on biosafety equipment, training, monitoring, and external quality verification. In compared to standard solid media, the usage of innovative in-house manufactured bilayered media for fast mycobacterial culture has been proven to achieve a greater isolation rate than liquid cultures. In addition, methods employing variable specimen processing techniques such as filtration of cerebrospinal fluid (CSF) samples and USP protocol for sample processing have reported increase in culture yield on solid and liquid media [10].

Phage-based assays MTB's ability to support the growth of an invading mycobacteriophage is used in the phage-based assay. For MTB diagnosis, two basic phage-based approaches are used: (1) phage amplification within viable MTB cells, followed by detection of plaque growth due to progeny phages using helper cells, and (2) detection of light emitted by luciferase reporter phages by viable MTB cells. Although phage-based assays are straightforward to perform, they require a high-tech laboratory infrastructure. The turnaround time for phage-based assays is two days, compared to two hours for smear microscopy and up to two months for culture. A systematic review of bacteriophage-based assays for rapid MTB detection discovered high specificity (83%-100%) but variable sensitivity (21%-88%) [11]. Sensitivity and specificity for smear-positive specimens varied from 29% to 87% and 60% to 88%, respectively, while sensitivity and specificity for smear-negative specimens ranged from 13% to 78% and 89% to 99%. Furthermore, when sensitivity was compared to smear microscopy, the difference was quite variable, with about comparable specificity. FAST Plaque TB sensitivity and specificity were shown to be 93.1% and 88.2%, respectively, in a study conducted in Mumbai [12].

Nucleic acid amplification test assays:

Nucleic acid amplification test (NAAT) assays such as polymerase chain reaction (PCR) have been heavily relied on for rapid diagnosis and accurate identification of MTB complex directly from clinical specimens. Although a plethora of both commercial and in-house tests exist, each targets a different method to amplify a particular sequence of mycobacterial genome, specific for MTB complex species. Commercial assays are expensive, require skilled labor and a high-infrastructure laboratory. Thus, use of commercial NAAT for rapid TB diagnosis as a replacement for conventional tests is not recommended. In-house tests are usually developed in resource-limited settings as an alternative to commercial assays. A systematic review of in-house studies has shown that the analytical sensitivity of PCR was not significantly affected by the kind of DNA extraction protocol (physical or chemical) employed but the use of IS6110 as a PCR target and the use of nested amplification protocols significantly increased the diagnostic accuracy of PCR [13]. A number of Indian research laboratories have attempted to standardize an efficient, reliable PCR for diagnosis of both pulmonary and extrapulmonary TB, and have reported variable diagnostic accuracy for each different kind of gene being targeted [14]. Use of an in-house PCR (targeting gene encoding 38-kDa protein) has reported high accuracy for reliable diagnosis of extrapulmonary TB [15]. Also, amplification of shorter DNA fragments has been shown to achieve higher sensitivity in comparison to amplification of larger DNA fragments [16]. A recent study has reported the use of a single-tube multitarget, nested PCR assay for diagnosis of extrapulmonary TB with a sensitivity and specificity of 94.5% and 96.4% respectively, and the number of cases being reported positive increases with the increase in number of targeted genes [17]. Researchers in India have developed a multiplex PCR assay capable of simultaneously detecting MTB complex and NTM species from clinical specimens that has a higher reported diagnostic accuracy in comparison to both solid and liquid cultures [18].

Indirect Tests:

Serology:

Serologic tests rely on antibody recognition of MTB antigens by the humoral immune response, as opposed to antigen recognition by the cellular immune response. The major advantages of these tests are their speed (results may be available within hours) and technical simplicity compared to smear microscopy. Several commercial serologic tests differing in a number of features, including antigen composition, antigen source, chemical composition, extent and manner of purification of the antigen(s), and class of immunoglobulin detected (eg, IgG, IgM, or IgA) have been evaluated for rapid diagnosis of TB. However, a systematic review evaluating all commercially available serologic assays reported that none of the assays performed well enough (inconsistent sensitivity and specificity) to replace sputum smear microscopy, having little or no role in the diagnosis of pulmonary and extrapulmonary TB [19]. Based on this evidence, the WHO issued a negative recommendation based on the poor performance of all commercial serodiagnostics and the adverse impact of misdiagnosis and wasted resources on patients and health services when using these tests for the diagnosis of active TB [20]. A recent study that performed a cost-effective analysis for the use of serologic tests in comparison with other available diagnostic assays in India inferred that serology was costlier and less effective than MGIT culture and hence does not recommend its use as an additional diagnostic test after smear microscopy for TB [21].

Role of Imaging in Diagnosis and Management:

Imaging is important in the diagnosis and treatment of active TB. A chest radiograph is usually taken at the time of diagnosis; a single PA image is usually sufficient. A lordotic image or dual-energy radiography with bone subtraction can improve the representation of the lung apices [22]. Whether clinically suspected or not, imaging findings suggestive of active tuberculosis should necessitate rapid discussion with the referring clinician and placement of the patient in respiratory isolation until negative sputum samples are obtained.

If tuberculosis is not first suspected clinically, but radiographic or computed tomographic (CT) results are suggestive of active tuberculosis, then additional workup for active tuberculosis is indicated. Regardless of the rationale, any radiologic finding that suggests active tuberculosis should prompt rapid communication with the referring clinician so that patients can be placed in pulmonary isolation until sputum staining results are negative.

Isoniazid, rifampin, ethambutol, and pyrazinamide are part of a four-drug regimen. The duration of the continuation phase can vary based on the patient's risk of recurrence. During the continuation phase, isoniazid and rifampin are usually given simultaneously [23]. Patients with active tuberculosis who have cavitation on the initial chest radiograph and who, at the completion of the initiation phase of treatment, still demonstrate positive 2-month tuberculosis cultures are at a high risk of relapse and

should continue therapy for a total of 9 months. Thus, careful examination of the initial chest radiograph should be made for cavitary disease (Figure 2). Although CT is twice as sensitive as chest radiography in the detection of cavities and may be useful in raising suspicion for active tuberculosis, the decision about the length of treatment in the algorithm is based on the presence of cavities on the chest radiograph, rather than on the CT images. Patients without cavitation on the initial chest radiograph and patients with a negative 2-month culture may need therapy for a total of only 6 months. A chest radiograph should be obtained in all patients at the completion of treatment to establish a new baseline (Figure 3) [24].

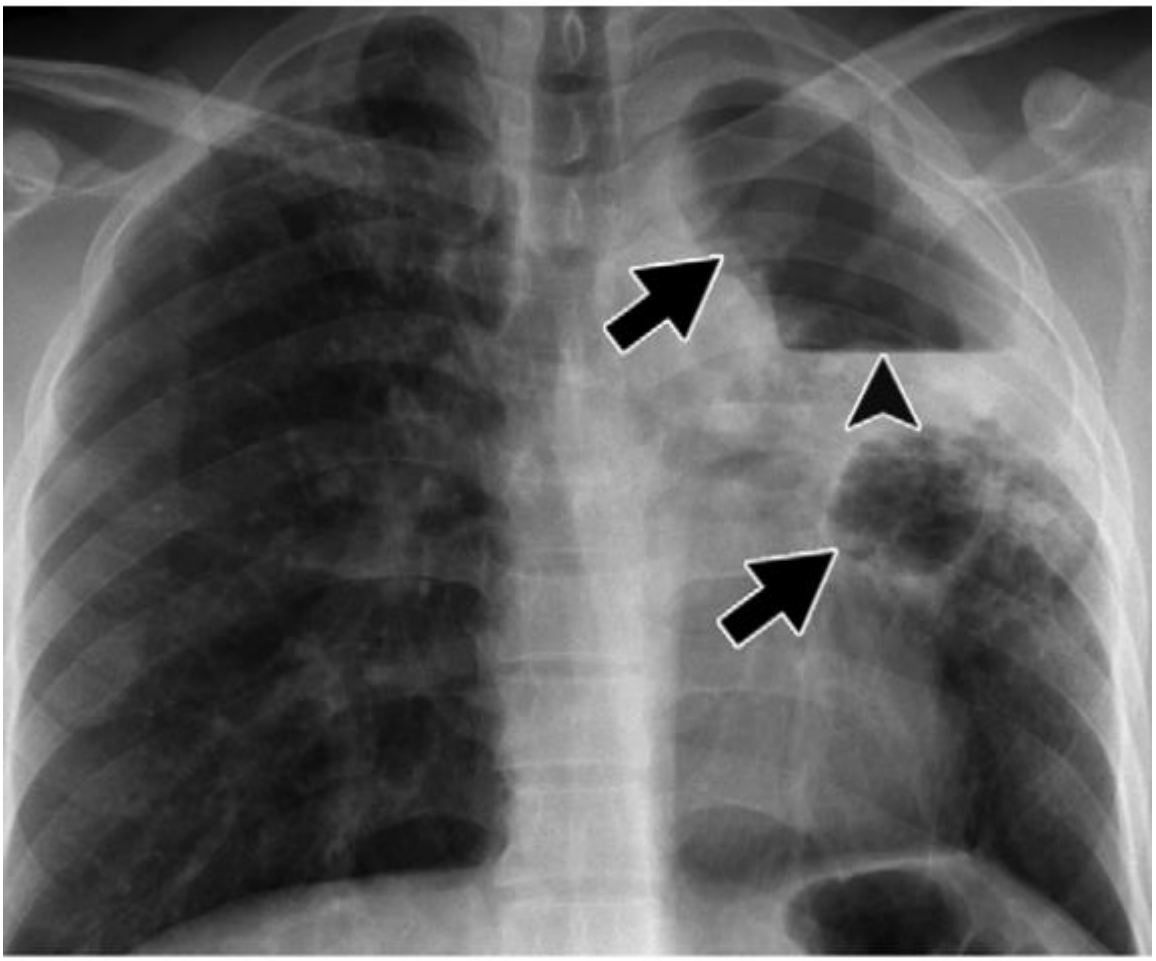

Figure 2: PA chest radiograph shows two left-sided cavitary lesions (arrows), with an air-fluid level in the larger lesion (arrowhead), and scattered reticulonodular opacities

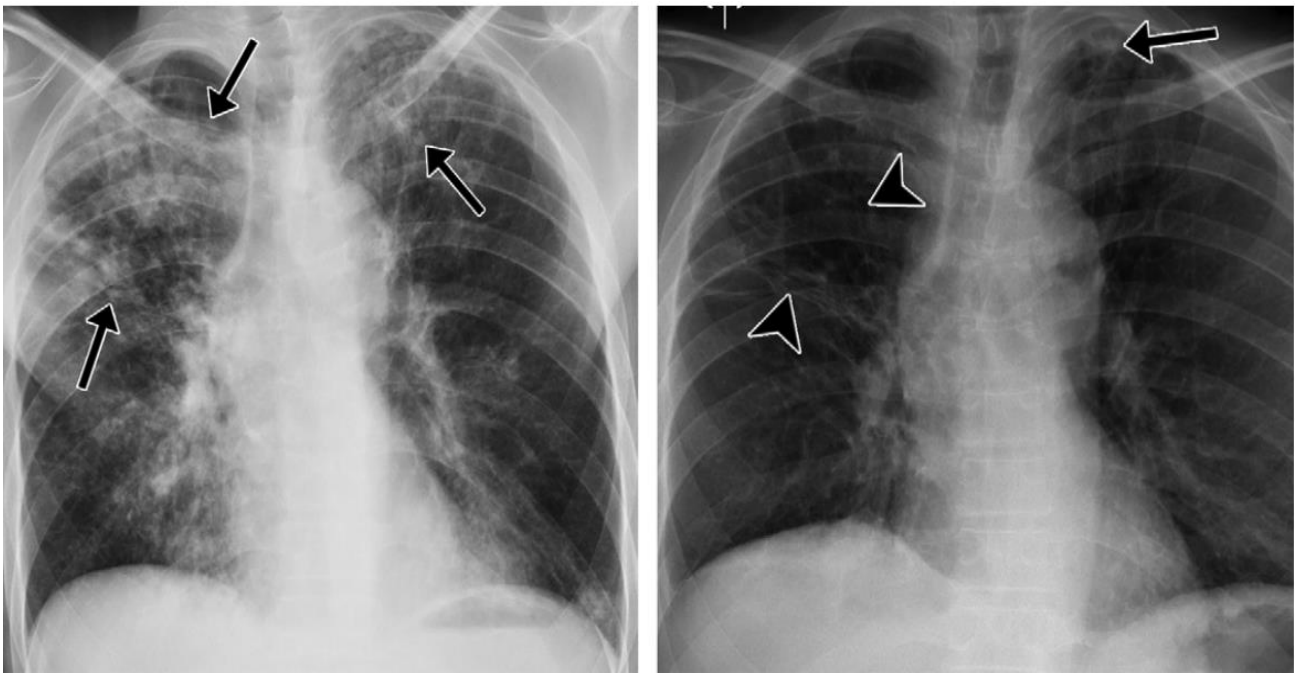

Figure 3: Pretreatment PA chest radiograph shows nodules and consolidations (arrows), predominantly in the bilateral apical and upper lung zones. (b) Posttreatment PA chest radiograph shows residual fibrosis (arrowheads) and nodular opacities (arrow), findings that represent this patient's new baseline.

CONCLUSION:

Tuberculosis is a major public health concern in both developing and industrialized nations. Radiologists must be knowledgeable about the imaging findings of pulmonary TB. It is critical to be aware of specific risk variables that can influence the likelihood and appearance of disease, such as vulnerability to exposure, altered immunity, pediatric age, and comorbidities. It is also critical to understand the function and limitations of laboratory testing, in addition to imaging and clinical evaluation, in establishing a diagnosis. Imaging aids in risk stratification in individuals with positive tuberculin skin test or interferon-release assay results by distinguishing latent infection, past inactive disease, and active disease.

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