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Research Article

Advances in the detection of extrapulmonary tuberculosis: A comprehensive narrative review

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Abstract

Tuberculosis (TB) is a highly infectious disease with high prevalence in the economically poor countries in the world with pulmonary and extrapulmonary manifestations. Though major involvement is pulmonary but extrapulmonary tuberculosis burden is quite high & requires a very strong index of suspicion with exhaustive workup for diagnosis. Due to delayed diagnosis and treatment, Extrapulmonary Tuberculosis (EPTB) seems to be more dangerous than Pulmonary Tuberculosis (PTB). EPTB can manifest itself in almost all parts of the body, producing a wide range of symptoms, making its detection tough. Early detection and timely treatment are necessary to prevent the worsening of the symptoms. Newer diagnostic tests like CBNAAT, RT-PCR, and gene sequencing have been introduced over recent years to improve the quality of assessment of this disease. While traditional diagnostic tests like culture, microscopy, and tuberculin tests take days to months to yield results, CBNAAT gives results in only 2 hours, thus making the prognosis better. However, their access is still limited to majorly developed and developing countries, being costlier than the traditional methods. This review focuses on various diagnostic procedures available for the diagnosis of EPTB.

Introduction

Tuberculosis (TB) is a transmissible disease caused by *Mycobacterium tuberculosis*. It is curable with the availability of effective antibiotics. However, timely diagnosis is essential to prevent its dissemination to other organs or advancement into Multidrug-resistant TB (MDR-TB) and extensively drug-resistant TB (XDR-TB). Although a fall has been seen in the overall cases over the recent years, the burden of Rifampicin-resistant TB (RR-TB) and Multidrug-resistant TB (MDR-TB) is increasing globally. There is a tremendous amount of evidence on the increasing mortality rate in extrapulmonary TB patients [1-3]. According to the Global Tuberculosis Report 2020, in 2019, an estimated 1.4 million cases succumbed to the infection out of the 10 million infected [4].

The disease manifests itself as Pulmonary TB (PTB) affecting the lungs and Extra-Pulmonary TB (EPTB) affecting various organs and tissues like the spine, heart, lymph nodes, brain, kidney, bones, etc. EPTB accounts for 15% - 20 % of HIV-negative TB cases, while the count increases to 40% - 50% in HIV-TB coinfection. Lymph nodes are the most commonly affected structures, followed by the pleura. Since EPTB manifests itself in different regions of the body, producing various symptoms, the diagnosis of EPTB using conventional methods like microscopy and culture becomes tough. The severity and mortality increase due to the delay in diagnosis and treatment [5].

As pulmonary TB accounts for maximum cases and mortality since ancient times, the topic has been heavily researched in contrast to extrapulmonary TB, which has gained

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attention in the past few years due to advancements in the medical field. The diagnosis of scattered extrapulmonary TB lesions becomes significantly important in dealing with EPTB cases. Although literature exists on this topic the diagnostic procedures in EPTB, this area has scope for more exploration as the new circulating strains can invade unexpected tissues in the body. Through this review article, we discuss the conventional as well as the modern techniques that can be used for the diagnosis of EPTB. Specimen collection from various sites and their processing have been discussed, followed by traditional methods like microscopy and culture. We have also discussed the CBNAAT, tuberculin skin test, tests for humoral immunity, and *in vitro* gamma interferon tests for the detection of EPTB. EPTB and HIV coinfection have also been discussed briefly in the subsequent section.

Detection of mycobacterium Tuberculosis

The detection of mycobacteria in extrapulmonary TB was earlier done using conventional methods, which include microscopy and culture of the bacteria from respective tissues. These methods are relatively cheap but time-consuming. The tuberculin skin test is extensively used in some areas but does not suggest active infection and is not useful in endemic areas. With the advent of technology, methods like the Cartridge-based Nucleic Acid Amplification Test (CBNAAT), Line Probe Assay (LPA), and Pyrosequencing tests have developed. These tests yield results in very little time compared to the traditional methods.

Types of specimens

Depending on the history and clinical presentation of the case, the specimen is collected from the site of suspected TB and screened for the presence of tuberculous bacteria. In cases of Lymph Node TB, the specimen is obtained from the orthostatic drainage of intra-articular fluid by Fine Needle Aspiration Cytology (FNAC) or biopsy. In cases of Pleural TB, pleural fluid is collected. However, induced sputum and pleural biopsy yield better results. In cases of CNS TB, a CSF sample is obtained by lumbar puncture. For suspected cases of Bone and Joint TB, a biopsy is done, and a fine needle aspirate of the lesions is obtained. In cases of Genitourinary TB, three early morning urine samples are obtained, while for GI and peritoneal TB, peritoneal fluid, and endoscopic mucosal biopsies are the specimens of choice [6] (Table 1).

Specimen processing

The direct (unconcentrated) specimen is widely used for the detection of MTB by smear microscopy in developed and underdeveloped countries. Smear microscopy of unconcentrated specimens is easy, less time-consuming, and not very costly, besides being highly specific for the tuberculous bacteria. However, the unconcentrated samples obtained from various body parts may contain a very low bacterial load, thus resulting in its low sensitivity and low accuracy. Therefore, processing of the specimens is recommended to obtain more accurate results, especially in cases of CNS TB and peritoneal TB [8].

Direct smears prepared from the specimens are subjected to the standard NALC-NaOH digestion-decontamination method (Modified Petroff's method), in which 2% NaOH and 1.45% sodium citrate contain 0.5% NALC are adequately mixed with the specimen. Phosphate buffer saline (pH 6.8) is added, and the mixture is centrifuged at 3000x for 15 minutes. The supernatant is removed, the remaining portion is re-suspended in 1.5 ml phosphate buffer saline, and the finally obtained suspension is used to prepare smears for microscopy and culture [9]. Specimen processing is required for LPA, Gene Sequencing & AFB Culture but not for AFB microscopy.

Acid-fast bacilli microscopy

Mycobacteria are acid-fast in nature. Pleural fluid, CSF, pus, urine sediments, and other specimens collected for the screening of EPTB are stained using Ziehl Neelsen Stain after concentration and decontamination. The smears are examined for the presence of pink-colored acid-fast mycobacteria under the oil emersion objective lens. The smears are graded as negative, scanty, +1, +2, and +3 according to the International Union against Tuberculosis and Lung Disease Scale [10,11] (Table 2).

Acid-fast bacilli culture

Acid-fast culture is the gold standard method for the detection of MTB. It can detect as low as ten bacilli/ml of the specimen. The specimens are inoculated on Lowenstein Jensen (LJ) Medium and incubated aerobically at 37 C for 2 - 8 weeks). Nowadays, BACTECT MGIT 960 is preferred over Lowenstein Jensen (LJ) and this can be attributed to the fact that it offers susceptibility testing of various drugs. The bacteria on the culture medium are confirmed as MTB using standard biochemical tests like niacin production, nitrate reduction, and catalase.

Methods to detect drug susceptibility for M.TB

There are two types of methods for drug susceptibility testing for mycobacterium tuberculosis.

Phenotypic method and Molecular method. The phenotypic method is a conventional one. It includes Lowenstein Jensen

Table 1: Comparison of pooled sensitivity and specificity of induced sputum versus bronchoscopy [7].

	Pooled Sensitivity (95% CI)	Pooled Specificity (95% CI)
Sputum Induction	0.72 (0.66 - 0.77)	1.00 (0.99 - 1.00)
Bronchoscopy	0.70 (0.64 - 0.75)	1.00 (0.99 - 1.00)

Table 2: Comparison of pooled sensitivity and specificity of induced sputum versus bronchoscopy [12].

	Gene Xpert/Xpert MTB/RIF		Xpert Ultra	
	Pooled Sensitivity	Pooled Specificity	Pooled Sensitivity	Pooled Specificity
CSF	71%	97%	89%	91%
Pleural fluid	50%	99%	75%	87%
Lymph Node Fluid	82%	96%	70%	100%
RIF Resistance	97%	99%	100%	100%

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Medium (solid culture), BACTEC 460TB (liquid culture), and MGIT 960 (liquid culture). Molecular methods involve Line Probe Assay, Xpert MTB/RIF, and MTBDRplus assay.

Median time to M. tuberculosis detection was substantially less with both the MTBDR plus (5 days) and Xpert (2 days) assays as compared to solid culture (33 days) and liquid culture (9 days).

Molecular methods (Line Probe Assay, Xpert MTB/RIF, and GenoType MTBDRplus assays) perform well in detecting TB and rifampin resistance and have substantially shorter turnaround time as compared to culture [13].

In comparison to the BACTEC 460TB, the MGIT 960 system is a more accurate alternative method for M. tuberculosis DST against INH and streptomycin. However, liquid culture-based methods, particularly the MGIT 960 system, are incapable of detecting low-level but clinically significant rifampicin resistance. Thus to detect RIF resistance, molecular methods of testing should be employed for all polydrug-resistant strains or when the suspicion for resistance is high [14]. Also for ethambutol, molecular methods may be more accurate than MGIT 960 as there is a high possibility of false susceptibility with it [14]. Resistance to RIF is a critical determinant of treatment failure. When testing for drug resistance in TB, the most frequent scenarios for discrepancies between phenotypic and genotypic methods are the presence of silent mutations and heteroresistance. Specific mutations k/a disputed mutations are detected genotypically but give a RIF-sensitive result in phenotypic tests, especially in liquid media. These mutations affect the "fitness" of MTB, causing it to grow slowly in the drug's presence during the phenotypic DST, which results in it not being detected, mainly by MGIT 960. These mutations are associated with therapeutic failure when RIF resistance is not detected, so the MGIT system should be reconsidered as the gold standard for detecting resistance to this drug to reduce the frequency of disagreements between the results of phenotypic and genotypic diagnostic methods [15]. However, to reach a final interpretation of drug resistance, both molecular testing and phenotypic DST results must be considered collectively [16].

CBNAAT/RT-PCR

Cartridge-based Nucleic Acid Amplification Test (CBNAAT) is the most advanced and the only self-contained cartridge-based, fully automated DNA testing platform for the detection of EPTB/PTB that can also detect Resistance to Rifampicin (RIF TB) in less than two hours. It is highly specific as it uses three specific primers and some unique molecular probes for the diagnosis.

Samples like CSF, Pus Aspirate, Bronchoalveolar Lavage, and induced sputum, can be used for CBNAAT. A blood sample cannot be used for CBNAAT.

One part of the sputum sample from a suspected individual is mixed with two parts of NaOH and isopropanol. This mixture is maintained at room temperature with intermittent shaking for 15 min and then transferred to a cartridge placed in the GeneXpert/ CBNAAT machine. Then the sample is automatically filtered and washed. Organisms in the sample undergo ultrasonic lysis to release DNA. DNA molecules are then mixed with dry PCR reagents. A semi-nested real-time amplification and detection occur in an integrated reaction tube and a printable test result is obtained [17].

If M. tuberculosis is detected, the results also show if the person is sensitive to RIF or resistant to RIF. If this is unclear, the test is repeated [18].

This is an excellent technique as it gives more accurate results in a shorter time duration than all other tests that nearly take weeks. It hence allows diagnosed TB patients to get effective treatment sooner. Besides, it also saves the cost of unnecessary hospitalization and treatment by giving quick results in negative patients. Also, being primarily automated, it requires minimal training [18].

However, CBNAAT does not eliminate the need for other diagnostic tests. It is recommended to use them in combination with them, thus ensuring the availability of mycobacterial culture isolates for drug susceptibility testing and genotyping for further investigation.

Detection of the host response to M. Tuberculosis

Tuberculin skin test: Tuberculin Skin Test (TST) or Mantoux Test is the traditional test and denotes past infection with tubercle baciili.

It involves intradermal administration of tuberculin on the forearm, which is a Purified Protein Derivative (PPD-S) derived from M. Bovis by a method given by Siebert. In India, the use of PPD-RT (Research Tuberculin) 23 in combination with Tween 80 has been standardized [19].

The test yields results 48 - 72 h after the administration of a standard dose of 10 Tuberculin Units (TU) (0.1 ml). A positive test is indicated by the appearance of an induration (in mm) at the site of administration as a result of a delayed hypersensitivity reaction. Lymphokines released by the T cells sensitized by prior infection lead to induration formation by recruiting inflammatory cells and causing local vasodilation, edema, and fibrin deposition [19].

Taking into consideration multiple factors like age, co-morbid conditions, immunological status, prior BCG vaccination, etc., the induration's size, which is interpreted as positive, varies from 5 mm, 10 mm, and 15 mm, respectively. Though the tuberculin test has epidemiological significance and is used to diagnose latent TB infection, its specificity and sensitivity are still objectionable. A follow-up is necessary, and the interpretation has to be made with the utmost care by an expert to minimize errors. A false-positive test seen in low-risk individuals may be due to nontuberculous mycobacterial infection or inefficient TST administration. Prior administration of BCG vaccine to children has also been found to give false-positive TST for up to 4 years, and even ten years in some cases. False-negative tests are also obtained

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due to various reasons, including very recent or very old TB infections. Some individuals may rarely develop anaphylactic reactions, foreign body reactions, redness, local lymphangitis, and adenitis post-PPD administration as adverse effects [19].

Tests for humoral immunity: The tests for humoral immunity include the detection of antibodies like Lipoarabinomannan (LAM), which is a component of the mycobacterial cell wall. A60, 38 Kd, and 16 Kd are the other antibodies screened for their presence in cases of EPTB. However, these tests are not very reliable and hence are generally not the diagnostic preference in hospitals [8,20].

The immune-chromatographic TB LAM Ag rapid assay (Alere Inc.) detects LAM antibodies in the Urine. Though the test is simple and economical, it may show false positives due to the contamination of the urine specimen with dust or feces. A negative result doesn't rule out the possibility either. It can also be helpful in detecting EPTB in HIV-positive patients [20,21].

***In vitro* gamma-interferon tests:** *In vitro*, gamma-interferon assay (IGRA) /QuantiFERON-TB Gold (QFT-G) is a new approach approved by the FDA to detect TB infection. It is principally based on the detection of IFN-γ produced by T cells of individuals sensitized with TB antigens on re-encounter with TB antigens introduced into the blood of suspected individuals [22]. Earlier, the antigens used were obtained from Purified Protein Derivatives (PPD). However, they are now being replaced by synthetic antigens that are peptides that represent two mycobacterial proteins, viz. early secretory antigenic target-6 (ESAT-6) and culture filtrate protein-10 (CFP-10). These synthetic peptide antigens give more specific and accurate results than the tests involving PPD [22].

The process involves two steps- [1] Introduction of synthetic antigens and mitogen into the blood and incubating it overnight. (M avium is introduced for T lymphocyte stimulation) [2] Quantification of IFN-γ from plasma supernatant using ELISA.

ESAT-6 and CFP-10 are not present in any BCG vaccines around the globe; hence, false-positive tests are not expected due to vaccination, unlike in other tests like TST. Besides, these antigens are also quite specific to M tuberculosis and are not shared by the majority of nontuberculous bacteria. Hence are less likely to show cross-reactions or false-positive results. This test is more specific and equivalently/more sensitive than TST and is expected to entirely replace it in the coming years in the settings of diagnosis of latent TB, and screening prior to administration of biologicals. IGRAs are very well used in latent TB but are unreliable in diagnosing active TB as they cannot distinguish between the two.

Diagnosis of TB in HIV-infected patients: TB infection being the leading cause of death in HIV co-infected individuals is hard to diagnose due to its extrapulmonary manifestations and low sensitivity of the standard diagnostic tests. The cheaper and most extensively used methods include (A) Smear microscopy- Smears prepared from infection samples are stained with Ziehl Neelsen stain and viewed under a fluorescent microscope. (B) Mycobacterial Culture- Traditional method that uses solid agar or liquid culture and allows Drug Susceptibility Testing (DST), besides tracking transmission during outbreaks. One particular example of a liquid culture system is MGIT. It was created in the United States by a company named Becton Dickinson (BD). It consists of a tiny tube filled with a solution that the so-called "medium" can grow TB bacteria in. The medium is an oxygen-containing special solution. After that, a TB drug is introduced. The TB bacteria are then added (for instance, from a sample of sputum), and the mixture is left in the tube for a few days. The time given for the bacterium to grow is known as the "incubation period" by investigators. When the oxygen in the tube is reduced, a special substance at the bottom of the tube begins to glow (scientists refer to this phenomenon as fluorescence). The oxygen is consumed by the TB bacteria as they multiply and "breathe." The tube is observed using a special light to determine whether or not the oxygen has been consumed and fluorescence is visible at the tube's bottom. If the bacteria in the tube are susceptible to the TB medication, the medication will suppress their growth. Because there are no bacteria to consume the oxygen, the tube won't fluoresce. If so, this medication can be used to treat the patient. The TB drug in the tube won't work if the TB bacterium is resistant to it, so it will grow instead. After a few days, the tube will begin to fluoresce as a result of the bacteria's growth depleting the oxygen. This medication should not be used to treat the patient in this situation because it will have no effect. For up to 42 days, a tube is watched to see if it contains developing TB bacteria and begins to fluoresce.

The newly developed molecular methods like NAATs, including Xpert MTB/RIF and Loop-mediated isothermal Amplification test assay (LAMP), are more accurate in detecting paucibacillary bacteria. Although these tests are more sensitive than the traditional methods and give results in less time, they are not used very frequently as they require expensive setups and high-level maintenance. Another method that detects antigens from the Urine of HIV-TB co-infected patients using the Lipoarabinomannan Lateral Flow Assay (LAM) method can be preferably used in high-burden countries. LAM is being approved by WHO for CD4 count <100/mm^3.

However, constant research is being done to develop diagnostic methods for rapid testing on a large scale with maximum sensitivity [23].

Discussion

Almost 10 million people were infected with Tuberculosis in the past year, with a higher incidence among HIV-positive patients. Nearly one-fourth of these cases had extrapulmonary manifestations. Mycobacterium tuberculosis can infect any part of our body except nails, hair, and teeth. Lymph nodes are almost involved in nearly half of the cases of Extra-Pulmonary TB. The clinical presentation of EPTB is insidious and varies according to the organ affected with or without lung involvement. This article addresses the major challenges involved in the diagnostic delay of extra pulmonary Tuberculosis.

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Early Diagnosis and treatment can significantly improve survival in addition to decreasing the morbidity and mortality associated with it. Imaging modalities like CT and MRI play a significant role in diagnosing Tuberculoma, gastrointestinal TB, and renal Tuberculosis, but the findings may be highly nonspecific. Tuberculin skin test and Interferon-Gamma Release Assay (IGRA) are not useful in diagnosing EPTB. The traditional Acid-fast staining and culture method has a low sensitivity making it a less reliable method in establishing a diagnosis.

Cytologic examination of serosal fluids based on the organ involved is also widely used nowadays. Adenosine Deaminase levels are elevated in EPTB patients making it one of the tools in diagnosis, yet the specificity of this method is still a concern. Interferon-gamma level measurement in the case of pericardial and pleural Tuberculosis has proven to be an efficient modality of diagnosis but is quite expensive and hence not widely used.

Nucleic Acid Amplification tests are an expeditious technique being used these days. Xpert MTB assay is a variant of NAAT which is now being recommended by the World Health Organization. Xpert MTB is considered a higher caliber test compared to the previously used diagnostic modalities, with a sensitivity rate of around eighty percent in diagnosing TB Lymphadenitis and Meningitis [24].

WHO recommends Isoniazid, Rifampin, Ethambutol, and Pyrazinamide for two months, followed by Isoniazid and Rifampin for the next four months. Any interruption during the treatment period may lead to the development of Drug-resistant Tuberculosis.WHO recommends a twelve-month regimen for treatment for TB Meningitis, two months of Intensive Regimen followed by a continued phase for the next ten months along with corticosteroids [25].

Conclusion

The gold standard method for the detection of Extra pulmonary TB remains the bacterial culture. As it is time-consuming, methods like CBNAAT using GeneXpert can be used in an emergency for early detection. The limitation of the availability of modern techniques in underdeveloped countries leads to late detection and thus increased severity of the disease. It can also detect resistance against Rifampicin, thus helping in delivering proper treatment. Antibody detection is also a good method to test the presence of MTB, but it does not show very promising results in systematic reviews and meta-analyses.

References

1. Addo SO, Mensah GI, Mosi L, Abrahams A, Bonfoh B, Kazwala R, Zinsstag J, Addo KK. Trends in extrapulmonary TB cases at three teaching hospitals in Ghana, 2008-2017. Public Health Action. 2021 Mar 21;11(1):26-32. doi: 10.5588/pha.20.0061. PMID: 33777718; PMCID: PMC7987251.

2. Singh P, Saket VK, Kachhi R. Diagnosis of TB: From conventional to modern molecular protocols. Front Biosci (Elite Ed). 2019 Jan 1;11(1):38-60. doi: 10.2741/E845. PMID: 30468637.

3. Hayward SE, Rustage K, Nellums LB, van der Werf MJ, Noori T, Boccia D, Friedland JS, Hargreaves S. Extrapulmonary tuberculosis among migrants in Europe, 1995 to 2017. Clin Microbiol Infect. 2021 Sep;27(9):1347.e1-1347.e7. doi: 10.1016/j.cmi.2020.12.006. Epub 2020 Dec 19. PMID: 33352301; PMCID: PMC8437049.

4. Global tuberculosis report 2020. https://www.who.int/publications-detail-redirect/9789240013131

5. Sharma SK, Mohan A. Extrapulmonary tuberculosis. Indian J Med Res. 2004 Oct;120(4):316-53. PMID: 15520485.

6. Norbis L, Alagna R, Tortoli E, Codecasa LR, Migliori GB, Cirillo DM. Challenges and perspectives in the diagnosis of extrapulmonary tuberculosis. Expert Rev Anti Infect Ther. 2014 May;12(5):633-47. doi: 10.1586/14787210.2014.899900. Epub 2014 Mar 20. PMID: 24717112.

7. Luo W, Lin Y, Li Z, Wang W, Shi Y. Comparison of sputum induction and bronchoscopy in diagnosis of sputum smear-negative pulmonary tuberculosis: a systemic review and meta-analysis. BMC Pulm Med. 2020 May 25;20(1):146. doi: 10.1186/s12890-020-01192-w. PMID: 32450826; PMCID: PMC7249394.

8. Steingart KR, Ng V, Henry M, Hopewell PC, Ramsay A, Cunningham J, Urbanczik R, Perkins MD, Aziz MA, Pai M. Sputum processing methods to improve the sensitivity of smear microscopy for tuberculosis: a systematic review. Lancet Infect Dis. 2006 Oct;6(10):664-74. doi: 10.1016/S1473-3099(06)70602-8. PMID: 17008175.

9. Uddin MK, Chowdhury MR, Ahmed S, Rahman MT, Khatun R, van Leth F, Banu S. Comparison of direct versus concentrated smear microscopy in detection of pulmonary tuberculosis. BMC Res Notes. 2013 Jul 25;6:291. doi: 10.1186/1756-0500-6-291. PMID: 23885922; PMCID: PMC3733684.

10. Abdelaziz MM, Bakr WM, Hussien SM, Amine AE. Diagnosis of pulmonary tuberculosis using Ziehl-Neelsen stain or cold staining techniques? J Egypt Public Health Assoc. 2016 Mar;91(1):39-43. doi: 10.1097/01.EPX.0000481358.12903.af. PMID: 27110859.

11. Detjen AK, DiNardo AR, Leyden J, Steingart KR, Menzies D, Schiller I, Dendukuri N, Mandalakas AM. Xpert MTB/RIF assay for the diagnosis of pulmonary tuberculosis in children: a systematic review and meta-analysis. Lancet Respir Med. 2015 Jun;3(6):451-61. doi: 10.1016/S2213-2600(15)00095-8. Epub 2015 Mar 24. PMID: 25812968; PMCID: PMC4756280.

12. Kohli M, Schiller I, Dendukuri N, Yao M, Dheda K, Denkinger CM, Schumacher SG, Steingart KR. Xpert MTB/RIF Ultra and Xpert MTB/RIF assays for extrapulmonary tuberculosis and rifampicin resistance in adults. Cochrane Database Syst Rev. 2021 Jan 15;1(1):CD012768. doi: 10.1002/14651858.CD012768.pub3. PMID: 33448348; PMCID: PMC8078545.

13. Bablishvili N, Tukvadze N, Avaliani Z, Blumberg HM, Kempker RR. A comparison of the Xpert(®) MTB/RIF and GenoType(®) MTBDRplus assays in Georgia. Int J Tuberc Lung Dis. 2015 Jun;19(6):676-8. doi: 10.5588/ijtld.14.0867. PMID: 25946358; PMCID: PMC4562278.

14. Ahmad S, Mokaddas E, Al-Mutairi N, Eldeen HS, Mohammadi S. Discordance across Phenotypic and Molecular Methods for Drug Susceptibility Testing of Drug-Resistant Mycobacterium tuberculosis Isolates in a Low TB Incidence Country. PLoS One. 2016 Apr 20;11(4):e0153563. doi: 10.1371/journal.pone.0153563. PMID: 27096759; PMCID: PMC4838278.

15. Rafael LL, Raquel MS, Rogelio FA, Miroslava FP, Alejandra-Isabel JG, Paola RS. Discordant results between genotypic and phenotypic assays (Xpert MTB/RIF vs. BACTEC MGIT 960 system) for detection of RIF-resistant Mycobacterium tuberculosis isolates in a high burden region. Infect Genet Evol. 2021 Dec;96:105142. doi: 10.1016/j.meegid.2021.105142. Epub 2021 Nov 17. PMID: 34800711.

16. Yakrus MA, Driscoll J, Lentz AJ, Sikes D, Hartline D, Metchock B, Starks AM. Concordance between molecular and phenotypic testing of Mycobacterium tuberculosis complex isolates for resistance to rifampin and isoniazid in the United States. J Clin Microbiol. 2014 Jun;52(6):1932-7. doi: 10.1128/JCM.00417-14. Epub 2014 Mar 19. PMID: 24648563; PMCID: PMC4042757.

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17. Sachdeva K, Shrivastava T. CBNAAT: A Boon for Early Diagnosis of Tuberculosis-Head and Neck. Indian J Otolaryngol Head Neck Surg. 2018 Dec;70(4):572-577. doi: 10.1007/s12070-018-1364-x. Epub 2018 Apr 16. PMID: 30464918; PMCID: PMC6224834.

18. TB Diagnostic Tool: Xpert MTB/RIF Assay Fact Sheet | TB | CDC 2022. https://www.cdc.gov/tb/publications/factsheets/testing/xpert_mtb-rif.htm

19. Nayak S, Acharjya B. Mantoux test and its interpretation. Indian Dermatol Online J. 2012 Jan;3(1):2-6. doi: 10.4103/2229-5178.93479. PMID: 23130251; PMCID: PMC3481914.

20. Kunnath-Velayudhan S, Davidow AL, Wang HY, Molina DM, Huynh VT, Salamon H, Pine R, Michel G, Perkins MD, Xiaowu L, Felgner PL, Flynn JL, Catanzaro A, Gennaro ML. Proteome-scale antibody responses and outcome of Mycobacterium tuberculosis infection in nonhuman primates and in tuberculosis patients. J Infect Dis. 2012 Sep 1;206(5):697-705. doi: 10.1093/infdis/jis421. Epub 2012 Jun 25. PMID: 22732925; PMCID: PMC3491745.

21. Nicol MP, Spiers K, Workman L, Isaacs W, Munro J, Black F, Zemanay W, Zar HJ. Xpert MTB/RIF testing of stool samples for the diagnosis of pulmonary tuberculosis in children. Clin Infect Dis. 2013 Aug;57(3):e18-21. doi: 10.1093/cid/cit230. Epub 2013 Apr 11. Erratum in: Clin Infect Dis. 2014 Jul 1;59(1):145. PMID: 23580738; PMCID: PMC3703104.

22. Litwin CM. In vitro gamma interferon tests for the detection of tuberculosis infection. J Immunotoxicol. 2007 Jul;4(3):219-24. doi: 10.1080/15476910701385646. PMID: 18958731.

23. Méndez-Samperio P. Diagnosis of Tuberculosis in HIV Co-infected Individuals: Current Status, Challenges and Opportunities for the Future. Scand J Immunol. 2017 Aug;86(2):76-82. doi: 10.1111/sji.12567. PMID: 28513865.

24. Lee JY. Diagnosis and treatment of extrapulmonary tuberculosis. Tuberc Respir Dis (Seoul). 2015 Apr;78(2):47-55. doi: 10.4046/trd.2015.78.2.47. Epub 2015 Apr 2. PMID: 25861336; PMCID: PMC4388900.

25. Pascual-Pareja JF, Carrillo-Gómez R, Hontañón-Antoñana V, Martínez-Prieto M. Treatment of pulmonary and extrapulmonary tuberculosis. Enferm Infecc Microbiol Clin (Engl Ed). 2018 Oct;36(8):507-516. English, Spanish. doi: 10.1016/j.eimc.2017.10.018. Epub 2017 Nov 21. PMID: 29169641.

Citation: Howal P, Sahu S, Ganiyani MA (2023) Advances in the detection of extrapulmonary tuberculosis: A comprehensive narrative review. Arch Pulmonol Respir Care 9(1): 012-017. DOI: https://dx.doi.org/10.17352/aprc.000083