Let's Talk TB

A Series on Tuberculosis, A Disease That Affects Over 2 Million Indians Every Year

Extrapulmonary Tuberculosis:
New Diagnostics and New Policies

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Abstract

Clinical presentations of extrapulmonary TB (EPTB) is diverse, leading to missed cases and delayed diagnoses. Since the diagnosis of EPTB is often compromised by the paucibacillary nature of the disease, new diagnostic tools and policies have been eagerly awaited. At long last, new tools, and new policies are here. The International Standards for TB Care (ISTC) recommends that all patients, including children, who are suspected of having EPTB, should have appropriate specimens obtained from the suspected sites of involvement for microbiological and histological exam. The World Health Organization (WHO) has endorsed the use of Xpert MTB/RIF assay (Cepheid Inc., Sunnyvale, California), a cartridge based nucleic acid amplification test (NAAT), for EPTB. Xpert MTB/RIF is now considered a central test in the work-up of EPTB, and should be used along with existing tools such as microscopy, liquid cultures (which are the most sensitive technologies for MTB detection), and histopathology (biopsy) to arrive at the final diagnosis. Xpert is particularly useful in cerebrospinal fluid samples and in lymph node and other tissues. Once diagnosed, EPTB must be treated with standardized treatment regimens, as recommended by ISTC.

Key words: extrapulmonary tuberculosis; diagnosis; Xpert MTB/RIF; new policies

INTRODUCTION

Globally, tuberculosis (TB) remains a major public health concern with an estimated 10.4 million new cases and 1.7 million deaths reported in 2016.[1] India accounts for 25% of this global TB burden, and for a third of the 'missing cases' that do not get diagnosed or notified.[1]

Although reliable data from India are lacking, it is expected that 15 – 20% of all TB is extrapulmonary. Clinical presentations of extrapulmonary TB (EPTB) may be diverse, leading to missed cases and delayed diagnoses. The prevalence of EPTB is higher in HIV co-infected patients and children, two vulnerable groups that are well-known to represent even greater diagnostic challenges. Moreover, the consequences of some forms of ETPB (e.g., TB meningitis) may be life-threatening and thus timely diagnosis and initiation of appropriate therapy are crucial.

In India, there is a widespread belief, without population-based data, that TB is a major cause of infertility and this poses major diagnostic challenges for infertility specialists. Furthermore, chronic fevers of unknown origin are often suspected to be TB and treated empirically as such, but there are little data to verify if this is indeed the case.

Since the diagnosis of EPTB is often compromised by the paucibacillary nature of the disease, new diagnostic tools and policies have been eagerly awaited. At long last, new tools (i.e., Xpert MTB/RIF), and new policies are here. In 2013, the World Health Organization (WHO) endorsed the use of Xpert MTB/RIF assay (Cepheid Inc., Sunnyvale, California), a cartridge based nucleic acid amplification test (NAAT), for EPTB.[2] In March 2014, the 3rd edition of the updated International Standards for TB Care (ISTC)[3] and the first edition of the Standards for TB Care in India (STCI)[4] were released and both included new rec-

Table 1 – Accuracy of Xpert for EPTB samples and WHO recommendations on how Xpert should be used in each sample type

Sample	Sensitivity (compared to culture)	Specificity (compared to culture)	WHO Recommendations on the Use of Xpert
Cerebrospinal fluid (CSF)	81%	98%	Xpert is recommended as an initial diagnostic test in cerebrospinal fluid specimens for TB meningitis (strong recommendation given the urgency of rapid diagnosis).
Lymph nodes	83%	94%	Xpert is recommended as a replacement test for usual practice in specific non-respiratory specimens (lymph nodes and other tissues) for EPTB (conditional recommendation).
Pleural fluid	46%	99%	Pleural fluid is a suboptimal sample and pleural biopsy is preferred. While a positive Xpert result in pleural fluid can be treated as TB, a negative result should be followed by other tests.
Gastric lavage and aspirations	84%	98%	Xpert is recommended as a replacement test for usual practice in specific non-respiratory specimens (including gastric specimens) for EPTB (conditional recommendation).

Source of data: references 2 and 10
Definition of abbreviations: EPTB= Extra-pulmonary TB; WHO=World Health Organization; TB=Tuberculosis

ommendations for EPTB diagnosis.

The ISTC emphasizes the importance of seeking microbiological and histopathological diagnosis of EPTB, and underscores the critical need for collecting appropriate samples. ISTC recommends that all patients, including children, who are suspected of having EPTB, should have appropriate specimens obtained from the suspected sites of involvement for microbiological and histological exam.[3] In practice, this may mean collection of samples such as body fluids (cerebrospinal, pleural, ascitic fluid), lymph node and other tissues (e.g., endometrial tissue), and aspirates (e.g., gastric aspirate, pus). Patients being investigated for EPTB, particularly people living with HIV (PLHIV), should also receive sputum testing and a chest radiograph as they may also have asymptomatic or minimally symptomatic pulmonary TB (PTB).

In India, especially in the private sector, blood is popular as a sample for TB diagnosis.[5] This practice has no biological or clinical rationale, as there is currently no accepted, validated biomarker in the blood that can detect EPTB or PTB. Thus, there is no role for blood-based antibody tests, or for blood-based interferon-gamma release assays (IGRAs) such as TB Gold and TB Platinum. IGRAs were designed to diagnose latent TB infection.[6] Like the tuberculin skin test (i.e., Mantoux), they cannot distinguish between latent infection and active pulmonary or extrapulmonary disease.[7,8] The Indian government banned serological antibody tests in 2012, and STCI and ISTC discourage the use of IGRAs for active TB diagnosis.[3,4]

Both ISTC and STCI now recommend the Xpert MTB/RIF assay for PTB and EPTB in adults and children.[4,7] The Xpert MTB/RIF assay allows for rapid detection of MTB DNA along with confirmation of rifampin resistance using rpoB gene mutation testing. It is automated, very easy to use and produces results within 2 hours.

Based on an updated Cochrane systematic review, when used as an initial test replacing smear microscopy for pulmonary TB, Xpert MTB/RIF has an overall sensitivity of 88% and pooled specificity of 98%, as compared to culture.[9] The pooled sensitivity is 98% for smear-positive, culture-positive cases and 68% for smear-negative cases; the pooled sensitivity is 80% in PLHIV. Xpert MTB/RIF, when used as an initial test replacing phenotypic drug susceptibility testing, detects 95% of rifampicin-resistant TB cases with specificity of 98%.[9]

More recently, evidence has accumulated on the accuracy of Xpert MTB/RIF for various forms of EPTB. This was summarized in a recent meta-analysis by Denkinger and colleagues[10] and is shown in **Table 1**, along with the latest WHO recommendations on EPTB, which are reiterated in the ISTC.

Thus, Xpert MTB/RIF should now be considered a central test in the work-up of EPTB, and should be used along with existing tools such as microscopy, liquid cultures (which are the most sensitive technologies for MTB detection), and histopathology (biopsy) to arrive at the final diagnosis. WHO has produced stan-

dard operating procedures on how to process various types of EPTB samples, and laboratories should implement these procedures to ensure quality.[11] It is important to note that Xpert MTB/RIF should not be performed on blood samples. Once diagnosed, EPTB must be treated with standardized treatment regimens, as recommended by STCI and ISTC.

While new tools like Xpert and new policies like STCI and ISTC are now available, it is important to ensure that these are widely used in the private sector, which manages nearly half of all TB in India. In fact, EPTB in India may be managed predominantly in the private sector. It is well known that TB diagnostic and treatment practices in the private sector are highly variable and often do not confirm to national or international standards.[5,12-14] This is why new initiatives like STCI should be widely promoted in the private sector, along with appropriate education and monitoring of quality of TB care.[14]

A big hurdle for the use of high quality, WHO-endorsed TB tests like Xpert and liquid cultures has been their high cost in the private market.[15] This is because WHO-endorsed tests are available at specially negotiated low prices only to the public sector, and import duties also add to the costs. In addition, financial incentives and laboratory margins further increase the costs to put them beyond the reach of most patients.

Fortunately, in 2013 a new initiative was launched to improve the affordability of WHO-endorsed TB tests. Initiative for Promoting Affordable, Quality TB tests (IPAQT www.ipaqt.org) is a coalition of private labs in India, supported by non-profit agencies such as the Clinton Health Access Initiative, that has made several WHO-approved tests available at affordable prices to patients in the private sector.[15-17] Labs in IPAQT have access to lower, concessionary prices for the quality tests in exchange of their commitment to pass on the lower prices to patients.

Due to IPAQT, which uses a high-volume, low-margin model to drive costs down, the cost of Xpert is now reduced to Rs 2200 (maximum price labs can charge patients). The line probe assay (Hain Genotype MTBDRplus, Hain Lifescience, Germany) is now available at Rs 1800. Liquid cultures (e.g., MGIT from BD Diagnostics) are available at Rs 900. These prices are approximately 30 to 50% less than the private market prices before IPAQT was launched. TB cases diagnosed are notified to the government and all labs are accredited. Since its launch, IPAQT has steadily grown – with over 170 labs across India now providing these tests at affordable prices.

In conclusion, patients with all forms of TB deserve a complete and patient-centric solution.[18] Improving the quality of TB care and expanding access to rapid, accurate diagnosis for all forms of TB, and prompt initiation of appropriate therapy is an ethical imperative and must be prioritized. It is our hope that new tools like Xpert, and new policies like ISTC and STCI will facilitate changes in practice and improve the quality of TB care for patients in India, regardless of whether they are managed in the public or the private sector.

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CIS CME–Questions

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Questions

1. **Which of the following samples is not appropriate for a case of suspected tuberculous pleural effusion?**
   a. Blood
   b. Pleural fluid
   c. Pleural biopsy
   d. Sputum

2. **Which of the following diagnostics tests is endorsed by WHO for extrapulmonary TB?**
   a. Interferon-gamma release assay (IGRA)
   b. Tuberculin skin test (Mantoux)
   c. Xpert MTB/RIF
   d. Serological (antibody) TB tests

3. **Which of the following tests are banned by the government of India:**
   a. Sputum smear microscopy
   b. Polymerase chain reaction (PCR)
   c. Interferon-gamma release assay (IGRA)
   d. Serological (antibody) TB tests

4. **Interferon-gamma release assays (e.g., TB Gold) and Mantoux skin test cannot distinguish between latent infection and active (pulmonary or extrapulmonary) disease. True or False?**
   a. True
   b. False

5. **Of the following tests, which has the highest sensitivity for TB?**
   a. Smear microscopy
   b. Tuberculin skin test
   c. Liquid cultures
   d. Interferon-gamma release assay (IGRA)

6. **In which of the following specimens does Xpert MTB/RIF have the lowest sensitivity?**
   a. Lymph nodes
   b. CSF
   c. Gastric aspirates
   d. Pleural fluid

(See answers on the next page)

CIS CME–Answers

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Answers

1. **The correct answer is (a).** There is no validated blood test for pleural or any form of extrapulmonary tuberculosis. Other samples listed are useful to collect.

2. **The correct answer is (c).** In 2013, WHO endorsed the use of Xpert MTB/RIF for extrapulmonary TB.

3. **The correct answer is (d).** The Indian Government has banned the use, sale and import of all commercial serological (antibody-detection) TB tests. This includes ELISA as well as rapid antibody tests. The ban applies to domestic as well as imported serodiagnostics kits. The ban is based on a WHO policy that strongly recommends against the use of serological, antibody tests for TB. The International Standards for TB Care, and Standards for TB Care in India also discourage the use of serological TB tests.

4. **The correct answer is TRUE.** Neither Mantoux nor TB Gold can separate latency from active TB disease. Thus, they are discouraged for active TB diagnosis.

5. **The correct answer is (c).** Liquid cultures have the highest sensitivity.

6. **The correct answer is (d).** Xpert does not have high sensitivity in pleural fluid samples, and therefore should not be used alone. It should be used in combination with other tests such as pleural fluid/tissue cultures and biopsy.