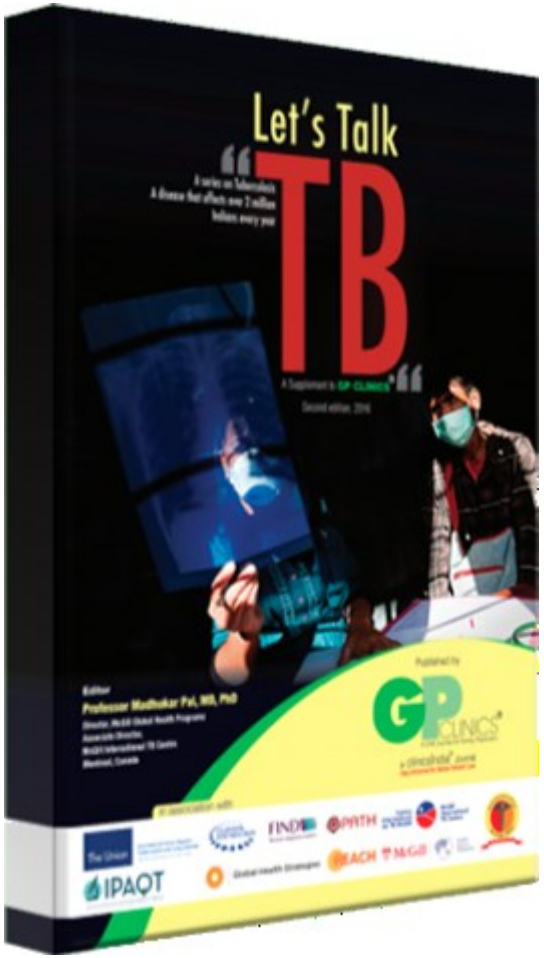

Let's Talk TB:

A Supplement to GP CLINICS

Chapter 6: Extrapulmonary Tuberculosis

New Diagnostics and New Policies

Authors: Ruvandhi Nathavitharana, MD, MPH—Author;
Madhukar Pai, MD, PhD—co-author and Series Editor

Global Picture of TB

- Globally, tuberculosis (TB) remains a major public health concern with an estimated 8.8 million new cases and 1.3 million deaths reported in 2012
  - India accounts for 25% of this global TB burden
  - And for a third of the 'missing cases' that do not get diagnosed or notified

Extrapulmonary TB

- Although reliable data from India are lacking, it is expected that 15 – 20% of all TB is extrapulmonary

EPTB

- 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
- The consequences of some forms of ETPB (e.g. TB meningitis) may be life-threatening
  - Timely diagnosis and initiation of appropriate therapy are crucial

Infertility

- In India there is a widespread belief (without population-based data) that TB is a major cause of infertility
  - Poses major diagnostic challenges for infertility specialists

Chronic Fevers

- Chronic fevers of unknown origin are often suspected to be TB and treated empirically as such
  - Little data to verify if this is indeed the case

New Tools and Policies

- Since the diagnosis of EPTB is often compromised by the paucibacillary nature of the disease, new diagnostic tools and policies have been eagerly awaited
- New tools (i.e. Xpert MTB/RIF) and new policies are here

Xpert MTB/RIF

- In 2013 the World Health Organization (WHO) endorsed the use of **Xpert MTB/ RIF** assay (Cepheid Inc, Sunnyvale, California)
  - Cartridge based nucleic acid amplification test (NAAT), for EPTB

ITSC and STCI

- In March 2014:
  - The 3rd edition of the updated International Standards for TB Care (ISTC) released
  - The 1st edition of the Standards for TB Care in India (STCI) released
- Both included new recommendations for EPTB diagnosis

ISTC

- 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

- In practice, this may mean collection of samples
  - Body fluids (cerebrospinal, pleural, ascitic fluid)
  - Lymph node
  - Other tissues (e.g. endometrial tissue)
  - 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)

Blood as a Sample

- In India (especially in the private sector) blood is popular as a sample for TB diagnosis
- 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)
  - TB Gold and TB Platinum.

IGRAs

- IGRAs were designed to diagnose latent TB infection
- Like the tuberculin skin test (i.e. Mantoux), they cannot distinguish between latent infection and active pulmonary or extrapulmonary disease
- The Indian government banned serological antibody tests in 2012
- STCI and ISTC discourage the use of IGRAs for active TB diagnosis

Xpert MTB/RIF

- Both ISTC and STCI now recommend the Xpert MTB/RIF assay for PTB and EPTB in adults and children
- 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

Cochrane Systematic Review

- 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
  - The pooled sensitivity is 98% for smear-positive, culture-positive cases, 68% for smear-negative cases
  - The pooled sensitivity is 80% in PLHIV

Cochrane Systematic Review

- 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%

Accuracy of Xpert MTB/RIF for EPTB

- 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 (**Table 1)** along with the latest WHO recommendations on EPTB

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

Xpert as the Central Test

- Xpert MTB/RIF should now be considered a central test in the work-up of EPTB
  - Should be used along with existing tools to arrive at the final diagnosis
    - Microscopy
    - Liquid cultures (which are the most sensitive technologies for MTB detection)
    - Histopathology (biopsy)
- WHO has produced standard operating procedures on how to process various types of EPTB samples
  - Laboratories should implement these procedures to ensure quality
- 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

Using the available New Tools

- 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
  - EPTB in India may be managed pre-dominantly in the private sector
- TB diagnostic and treatment practices in the private sector are highly variable and often do not confirm to national or international standards
  - New initiatives like STCI should be widely promoted in the private sector, along with appropriate education and monitoring of quality of TB care

Challenges

- High quality, WHO-endorsed TB tests like Xpert and liquid cultures
  - High cost in the private market
- WHO- endorsed tests are available at specially negotiated low prices only to the public sector, and import duties also add to the costs
- Financial incentives and laboratory margins further increase the costs to put them beyond the reach of most patients

IPAQT

- 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)**
  - A coalition of private labs in India, supported by non-profit agencies such as the Clinton Health Access Initiative
  - Made several WHO-approved tests available at affordable prices to patients in the private sector
  - 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

Prices due to IPAQT

- Due to IPAQT (which uses a high-volume, low-margin model to drive costs down)
  - The cost of Xpert is now reduced to Rs 2000 (maximum price labs can charge patients)
  - The line probe assay (Hain Genotype MTBDRplus, Hain Lifescience, Germany) is now available at Rs 1600
  - 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

IPAQT Growth

- Since its launch, IPAQT has steadily grown with over 75 labs across India now providing these tests at affordable prices

Complete Patient Care

- Patients with all forms of TB deserve a complete and patient-centric solution
- 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

Complete Patient Care

- 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

References

1. World Health Organization. Global Tuberculosis Control. *WHO Report 2013.* Geneva: WHO;2013.

2. World Health Organization. Policy update: automated realtime nucleic acid amplification technology for rapid and simultaneous detection of tuberculosis and rifampicin resistance: Xpert MTB/ RIF system for the diagnosis of pulmonary and extrapulmonary TB in adults and children 2013. Available at URL: http://apps.who.int/iris/ bitstream/10665/112472/1/9789241506335_ eng.pdf?ua=1. Accessed on 17 June, 2014.

3. TB CARE I. International Standards for Tuberculosis Care, 3rd edition. 2014. Available at URL: www.istcweb.org. Accessed on March, 2014.

4. World Health Organization (Country Office for India). Standards for TB Care in India. Available at URL: http://www.tbcindia.nic.in/pdfs/stci%20 Book_final%20%20060514.pdf. Accessed on 17 June, 2014.

5. Jarosawlski S, Pai M. Why are inaccurate tuberculosis serological tests widely used in the Indian private healthcare sector? A root-cause analysis.
J Epidemiol Global Health. 2012;2:39-50.

6. Pai M, Denkinger CM, Kik SV, Rangaka MX, Zwerling A, Oxlade O, et al. Gamma Interferon Re- lease Assays for Detection of Mycobacterium tuberculosis Infection. *Clin Microbiol Rev.* 2014;27:3-20.

7. Metcalfe JZ, Everett CK, Steingart KR, Cattamanchi A, Huang L, Hopewell PC, et al. Interferon-gamma release assays for active pulmonary tuberculosis diagnosis in adults in low- and middle-income countries: systematic review and meta-analysis. *J Infect Dis.* 2011; 204 (Suppl. 4): S1120-9.

8. Fan L, Chen Z, Hao XH, Hu ZY, Xiao HP. Interferon gamma release assays for the diagnosis of extrapulmonary tuberculosis: a systematic review and meta-analysis. *FEMS Immunol Med Microbiol.* 2012;65:456-66.

9. Steingart K, Schiller I, Horne DJ, Pai M, Boehme C, Dendukuri N. Xpert® MTB/RIF assay for pulmonary tuberculosis and rifampicin resistance in adults. *Cochrane Database Syst Rev.* 2014;1:CD009593.

10. Denkinger CM, Schumacher SG, Boehme CC, Dendukuri N, Pai M, Steingart KR. Xpert MTB/RIF assay for the diagnosis of extrapulmonary tuberculosis: a systematic review and meta-analysis. *Eur Respir J.* 2014;April 17.[Epubahead of print].

11. World Health Organization. Standard Operating Procedure (SOP): Specimen processing of CSF, lymph nodes, and other tissues for Xpert MTB/RIF. Available at URL: http://apps.who.int/iris/bitstream/10665/112469/1/9789241506700_eng.pdf?ua=1. Accessed on 17 June, 2014.

12. Achanta S, Jaju J, Kumar AM, Nagaraja SB, Shamrao SR, Bandi SK, et al. Tuberculosis management practices by private practitioners in Andhra Pradesh, India. *PLoS One.* 2013;13:e71119.

13. Udwadia ZF, Pinto LM, Uplekar MW. Tuberculosis management by private practitioners in Mum- bai, India: has anything changed in two decades? *PLoS ONE.* 2010; 5:e12023.

14. Pai M, Das J. Management of tuberculosis in India: time for a deeper drive into quality. *Natl Med J India.* 2013;26:e1-e4.

15. Pai M. Promoting affordable and quality tuberculosis testing in India. *J Lab Physicians.* 2013;5:1-4.

16. Kay M. Private firms form initiative to offer accurate and affordable TB tests. *BMJ.* 2013;346:f2161.

17. Iyer M. 70 labs in India cut TB test bill by half. Times of India 2014 March 22.

18. Pai M, Yadav P, Anupindi R. Tuberculosis con- trol needs a complete and patient-centric solution. *Lancet Global Health.* 2014;2:e189-e90.