

Extrapulmonary Tuberculosis: New Diagnostics and New Policies

Globally, tuberculosis (TB) remains a major public health concern with an estimated 8.8 million new cases and 1.3 million deaths reported in 2012.¹ 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% to 20% of all TB is extra-pulmonary. Clinical presentations of extra-pulmonary TB (EPTB) may be diverse, leading to incorrect and delayed diagnoses. The prevalence of EPTB is higher in human immunodeficiency virus (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 EPTB (such as, 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 supporting population-based data, that TB is a major cause of infertility and this poses a major diagnostic challenge for infertility specialists. Furthermore, chronic fevers of unknown origin are often suspected to be TB and treated empirically without any proof of diagnosis.

As the diagnosis of EPTB is often compromised by the paucibacillary nature of the disease, newer diagnostic tools and policies have been eagerly awaited. 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 recommendations for the diagnoses of EPTB.

The ISTC emphasises the importance of seeking microbiological and histopathological diagnosis of EPTB, and underscores the critical need for collecting appropriate samples. The *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 examination.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 those 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 specimen for diagnosis of TB.⁵ This

practice lacks any biological or clinical rationale. 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. The IGRAs were designed to diagnose latent TB infection.⁶ Like the tuberculin skin test (i.e., Mantoux), these cannot distinguish between latent infection and active- or extra-pulmonary disease.^{7,8} The Indian government banned serological antibody tests in 2012, and both *STCI* and *ISTC* discourage the use of IGRAs for the diagnosis of active TB.^{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 rifampicin resistance using *rpoB* gene mutation testing. It is automated, very easy to use and yields results within two hours.

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

More recently, evidence has accumulated on the accuracy of Xpert MTB/RIF for various forms of EPTB. This was summarised in a recent meta-analysis by Denkinger and colleagues¹⁰ and is shown in the table, along with the latest WHO recommendations on EPTB, which have been reiterated in the *ISTC*.

Thus, Xpert MTB/RIF should now be considered a central test in the work-up of EPTB, and may be used along with conventional tools, such as microscopy, liquid cultures (that are the most sensitive technologies for MTB detection), and histopathology (biopsy) to arrive at the final diagnosis. World Health Organization has developed standard operating procedures on how to process various types of EPTB samples, and laboratories should adopt 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 standardised 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 cases in India. It is

Table. 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	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

even likely that, 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 very widely and often do not confirm to national or international standards.^{5, 12-14} This is all the more reason 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 in the use of high quality, WHO-endorsed TB tests, like Xpert and liquid cultures has been their high cost in the private market.¹⁵ In contrast, WHO-endorsed tests are available at specially negotiated low prices in the public sector.

To overcome this hurdle, 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 laboratories 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 Laboratories in IPAQT have access to lower, concessionary prices for the quality tests in exchange for their commitment to pass on the lower prices to patients.

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 prioritised. 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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References

1. World Health Organization. Global Tuberculosis Control. *WHO Report 2013*. Geneva: WHO;2013.
2. World Health Organization. Policy update: automated real-time 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.tbccindia.nic.in/pdfs/stci%20Book_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 Release 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.[Epub ahead 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. Udhwadia ZF, Pinto LM, Uplekar MW. Tuberculosis management by private practitioners in Mumbai, 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 control needs a complete and patient-centric solution. *Lancet Global Health* 2014;2:e189-e90.

