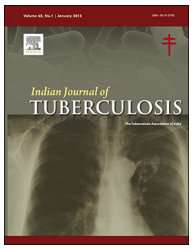
INDIAN JOURNAL OF TUBERCULOSIS

EDITORIAL BOARD

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: http://www.journals.elsevier.com/indian-journal-of-tuberculosis/



Editorial

Tuberculosis in children – Need for urgent roadmap under Revised National Tuberculosis Control Programme

The urgency of the problem of tuberculosis (TB) in children, which relegated in the shadows for centuries ever since mankind has known TB, seems to have finally got its much deserved global spotlight. The WHO has declared that the goal of reaching zero TB deaths among children worldwide is within our grasp.[1] The first-ever targeted roadmap outlines steps to end childhood TB deaths in 'The Roadmap for Childhood Tuberculosis: Towards Zero Deaths'.[2]

The WHO estimates TB in children accounts for 6–10% of all TB cases that occur globally every year, alarmingly rising up to as much as 40% in countries with a high rate of TB disease; at least 5 lakh children get sick with TB worldwide every year with more than 74,000 of them dying; these estimates only include those in Human Immunodeficiency Virus (HIV)-negative children, the incidence with AIDS catapulting to almost 500 times more accounting for about 30% of AIDS deaths.[1] There is increasing recognition of the global burden of TB in children as well as its impact on child health and now it is thought to be of a higher magnitude than what was hitherto reported. The new estimates using mathematical modeling indicate that over 650,000 children develop TB every year in the 22 High Burden-Disease countries (HBCs), almost 25% higher than the 2012 WHO estimates of 530,000 cases.[3] Researchers from Harvard have estimated that the total number of children newly infected with TB is twice that estimated by the WHO in 2011 and thrice of that which gets notified/year.[4] In 2012, 81,482 pediatric cases were notified in India accounting for 7% of all notified TB cases.[5] Pediatric TB reflects recent infection and therefore represents continuing transmission in the population and the prevalence of the disease in adults.

Several technical difficulties compound the challenges of diagnosing TB in children: diverse, relatively nonspecific clinical presentation, variable interpretation of overlapping clinical manifestations especially in the context of co-existing malnutrition/HIV, difficulty of obtaining specimens, variable interpretation of chest radiographs, paucibacillary disease, and relatively low rates of bacteriological confirmation. Hence, it is easy to overdiagnose as well as underdiagnose. Poverty, ignorance, and limited access to health care services compound the difficulties further. More recently, high-tech diagnostics approaches such as real-time PCR (GeneXpert/Xpert MTB/RIF), E-nose, and infrared spectroscopy are gaining relevance. With the GeneXpert which is a fully automated real-time DNA-based test, both TB and resistance to rifampicin can be detected in less than 2 h with minimal hands-on technical time. It is a simple diagnostic tool that could widely be implemented potentially impacting on TB control.[6] The GeneXpert assay can be utilized on nonsputum samples from patients with paucibacillary extra-pulmonary TB where sputum sampling is impractical, like in children and thus may yield improved diagnostic rates in them.[7] The recent WHO recommendation is to use Xpert MTB/RIF rather than conventional microscopy and culture as the initial diagnostic test in all children suspected to have multidrug-resistant (MDR)-TB or HIV-associated TB, or in cases of TB meningitis testing CSF; however, WHO cautions that access to conventional microscopy, culture, and drug susceptibility testing (DST) is still needed for monitoring of therapy, prevalence surveys, and/or surveillance and in cases where resistance to drugs other than rifampicin are suspected (including second-line anti-TB drugs).

WHO recommends the use of one sputum specimen for diagnostic testing, given the resource implications of using multiple specimens.[8] The Cochrane Diagnostic Test Accuracy (DTA) Review summarizes evidence from 18 cross-sectional, randomized, and cohort studies that included 7816 adult participants from 27 diverse centers, confirming the high sensitivity and specificity of Xpert MTB/RIF for detecting MTB in culture-positive sputum samples: for those studies that used Xpert MTB/RIF either for initial or add-on testing algorithms, specificity was noted to be 98%; in patients with suspected smear-negative TB, sensitivity was 88% for initial testing and 67% for add-on testing; in patients with HIV infection, sensitivity was 80%. The high sensitivity of Xpert MTB/RIF makes this diagnostically useful in the diagnosis of TB in people with HIV co-infection, where the sensitivity of smear microscopy alone is low. Rifampicin resistance can be detected accurately (sensitivity 94%; specificity 98%) within

a few hours making Xpert MTB/RIF a boon, given the obstacles of diagnosing drug resistance using traditional methods.[9] A feasibility and impact study in India, using a single Xpert MTB/RIF test offered for TB case finding at decentralized laboratories across 18 sites, found a 7.2% increase in the diagnostic yield compared to smear microscopy; 22,345 pulmonary TB cases and 1738 suspected drug-resistant (DR-TB) cases were tested between March and October 2012. 4422 of the 22,345 TB suspected cases were confirmed as having TB when the Xpert MTB/RIF tests were used, with a 20% positivity rate as compared to the smear microscopy that yielded a positivity rate of only 12.8% on the same sputum specimens; Xpert MTB/RIF also diagnosed 569 cases of rifampicin-resistant TB (293 among the suspected TB cases and 276 among suspected DR-TB cases). Regarding the feasibility of deploying Xpert MTB/RIF at decentralized level, the study found that each of the 18 sites could do 5000 tests per month with minimally modified infrastructure and human resources and major cartridge wastage could be avoided if 2 h of back-up electricity could be supplied. The 93% interpretable results from the first test could be increased to 99% on a repeat test.[10]

It remains to be seen how this valuable tool can be integrated into national programmes in high burden countries, especially in areas and populations where it is most needed for early detection and management which is crucial to curtail this growing epidemic.

Also, a newly developed sputum-independent immunodiagnostic T-cell Activation Marker – Tuberculosis (TAM-TB) assay, a rapid and accurate blood test that yields results within 24 h featuring excellent specificity and similar sensitivity to culture, has the potential to improve the diagnosis of active TB in children.[11]

TB can be more severe and progress to death more rapidly in HIV-infected children. Both infections require multi-drug-therapies, making drug-to-drug interactions and drug toxicities and treatment adherence more complicated. Appropriately dosed new, shorter, all-oral fixed-dose-combinations with better safety and tolerability profile that are effective against all forms of TB and available in pediatric formulations are urgently needed in children to lower toxicity, pill burden, and frequency of medication administration, all factors extremely important for better adherence and clinical outcomes. These children should be followed carefully not only to ensure adequate nutrition/adherence and monitor side effects, but also to ensure treatment completion, minimizing the risk of emergence of drug-resistant disease thereby enhancing TB control.[12]

For the first time in over 40 years, a new TB drug with a novel mechanism of action – bedaquiline, a diarylquinoline antibiotic, was granted accelerated approval by the United States Food and Drug Administration in December 2012 as part of combination therapy to treat adults with multidrug-resistant pulmonary TB when other alternatives are not available.[13] It is important to include children early in clinical trials and many drugs and new compounds are currently under different phases of preclinical and clinical evaluation for the treatment and prevention of pediatric TB.[14]

An emerging threat is the rise of drug-resistant TB. A recent review provides contextualized estimates of MDR TB incidence in children to be about 32,000 in 2010 and also points out that all cases ever reported in literature represent only 2% of estimated new cases/year.[4] A study from Mumbai showed that the burden of drug-resistant TB among HIV-infected patients attending public ART-centers in Mumbai was alarmingly high, likely representing ongoing transmission in the community and health facilities.[15]

The WHO recommends isoniazid preventive therapy for child contacts of drug-sensitive TB patients,[8] but no such recommendation exists for child-contacts of drug-resistant TB patients. It is imperative to rapidly identify and screen all children exposed to household contacts of drug-resistant TB and either treat or put them on prophylactic therapy. It is very important to identify and validate TB drugs/regimens that can be used to prevent disease in these child-contacts of drug-resistant TB patients. Currently, they are treated empirically according to the drug susceptibility result of the likely source case as they are likely to become infected with the same resistant strains and often cultures cannot be obtained. One study found 6 months of daily ofloxacin, ethambutol, and high-dose isoniazid was well tolerated in children with household exposure to MDR TB and few children developed TB or died[16]; evaluation and substantiation with more studies could throw more light for preventive therapy in children exposed to MDR-TB. With rapid diagnosis and appropriate treatment, outcomes in majority of children with MDR TB and even extensively drug-resistant TB are good, despite limited pharmacokinetic data on second-line drugs.[17]

Children frequently escape the attention of TB control programs because children are ineffective transmitters. The fact that the morbidity and mortality of TB is higher in childhood and also acquisition of TB infection during childhood contributes to the future reservoirs of epidemics makes it imperative to identify and treat children and their families for TB elimination. There is an urgent need for a better preventive vaccine for TB as there has been escalation in incidence of TB despite good BCG coverage rates in many developing countries and also there is a potential for disseminated BCG disease in the context of HIV infection. Meticulous screening of children in high-risk situations with a high degree of suspicion and appropriate chemoprophylaxis/treatment can decrease the disease burden. The interruption of the chain of transmission of TB by providing effective treatment is the best way to prevent TB. From the public health point of view, the goals should be to reduce deaths, sickness, and prevent disease transmission, while simultaneously tackling the growing threat of drug-resistant TB. Mankind has suffered from TB since time immemorial and it is high time this scourge is curbed effectively thereby reducing human suffering as well as the socioeconomic burden it brings along with it on families, communities, and nations. The due recognition of the importance of childhood TB along with ongoing progress in diagnostic, management, and preventive strategies, coupled with a strong family/community-oriented approach to contact-tracing with effective interruption of transmission will go a long way in curbing this disease which is largely preventable and curable. The importance of providing ongoing psychosocial support to help ameliorate the negative effects of psychological, academic, and financial impacts on these children and their families cannot be overemphasized. It is therefore essential that revised national tuberculosis programme encompasses all these factors including MDR issues in

pediatric population and develops the road map for its early control.

Conflicts of interest

The author has none to declare.

REFERENCES

1. Global Tuberculosis Report 2013. *World Health Organization*. Available from www.who.int/tb/publications/global_report/en/. Accessed 11.11.13.
2. *The Roadmap for Childhood Tuberculosis: Towards Zero Deaths*. Available from http://apps.who.int/iris/bitstream/10665/89506/1/9789241506137_eng.pdf. Accessed 11.11.13.
3. Dodd PJ, Gardiner E, Coghlan R, et al. Burden of childhood tuberculosis in 22 high-burden countries: a mathematical modelling study. *Lancet Glob Health*. 2014;2(8):e453–e459. http://dx.doi.org/10.1016/S2214-109X(14).70245-1.
4. Jenkins HE, Tolman AW, Yuen CM, et al. Incidence of multidrug-resistant tuberculosis disease in children: systematic review and global estimates. *Lancet*. 2014;383(9928):1572–1579. http://dx.doi.org/10.1016/S0140-6736(14).60195-1.
5. Revised National Tuberculosis Control Program. *TB India 2013, RNTCP Annual Status Report*. Available from http://www.tbcindia.nic.in/pdfs/tb%20india%202013.pdf; 2013.
6. Lawn SD, Nicol MP. Xpert MTB/RIF assay: development, evaluation and implementation of a new rapid molecular diagnostic for tuberculosis and rifampicin resistance. *Future Microbiol*. 2011;6(9):1067–1082.
7. Vadwai V, Boehme C, Nabeta P, et al. Xpert MTB/RIF: a new pillar in diagnosis of extrapulmonary tuberculosis? *J Clin Microbiol*. 2011;49:2540–2545.
8. World Health Organization. *Guidance for National Tuberculosis Programmes on the Management of Tuberculosis in Children*. 2nd ed. Geneva: WHO; 2014. Available from http://www.who.int/tb/publications/childtb_guidelines/en/. Accessed 26.06.14.
9. Steingart KR, Sohn H, Schiller I, et al. Xpert® MTB/RIF assay for pulmonary tuberculosis and rifampicin resistance in adults. *Cochrane Database Syst Rev*. 2013;CD009593. http://dx.doi.org/10.1002/14651858.CD.93.0095.pub2 [January 31].
10. Raizada N. Experience with implementation of Xpert MTB/RIF in India. In: *43rd Union World Conference on Lung Health*. Kuala Lumpur2012.
11. Portevin D, Moukambi F, Clowes P, et al. Assessment of the novel T-cell activation marker–tuberculosis assay for diagnosis of active tuberculosis in children: a prospective proof-of-concept study. *Lancet Infect Dis*. 2014;14(10):931–938. http://dx.doi.org/10.1016/S1473-3099(14).7088.4-9.
12. Lala MM. HIV related lung diseases in children. In: Arora VK, ed. In: *Manual on Tuberculosis, HIV & Lung Diseases: A Practical Approach*. India: Jaypee Brothers Medical Publishers; 2009:320–335.
13. Walker J, Tadena N. J and J tuberculosis drug gets fast-track clearance. *The Wall Street Journal*. 2013. January 2 [Last cited on 17.03.13]. Available from http://online.wsj.com/article/SB10001424127887323320404578213421059138236.html.
14. McKenna L. *Playing Catch-Up: The Pediatric Tuberculosis Treatment Pipeline*, July 2014. Available from http://www.pipelinereport.org/sites/g/files/g575521/f/201407/TB%20Pediatric%20Treatment.pdf. Accessed 26.02.15.
15. Isaakidis P, Das M, Kumar AMV, et al. Alarming levels of drug-resistant tuberculosis in HIV-infected patients in metropolitan Mumbai, India. *PLoS ONE*. 2014;9(10):e110461. http://dx.doi.org/10.1371/journal.pone.2014.0110461.
16. Seddon JA, Hesseling AC, Finlayson H, et al. Preventive therapy for child contacts of multidrug-resistant tuberculosis: a prospective cohort study. *Clin Infect Dis*. 2013;57(December (12)):1676–1684. http://dx.doi.org/10.1093/cid/cit655.
17. Schaaf HS, Garcia-Prats AJ, Hesseling AC, et al. Managing multidrug-resistant tuberculosis in children: review of recent developments. *Curr Opin Infect Dis*. 2014;27(June (3)):211–219. http://dx.doi.org/10.1097/QCO.0000000000000062.

Mamatha M. Lala[a,b]

[a]*Consultant: Pediatric HIV Telemedicine, Pediatric Center of Excellence for HIV Care – LTMMC & LTMGH, India*

[b]*Medical Advisor and Consultant Pediatrician – Committed Communities Development Trust (CCDT), Mumbai Smiles, Society for Human and Environmental Development (SHED), India*

E-mail address: mamathalala@gmail.com (M.M. Lala)

Available online 9 October 2015

http://dx.doi.org/10.1016/j.ijtb.2015.09.011

0019-5707/

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: http://www.journals.elsevier.com/indian-journal-of-tuberculosis/

Viewpoint

Positioning the CXR – As a triage test for tuberculosis

Lalit Kant *

Former Head, Division of Epidemiology & Communicable Diseases, Indian Council of Medical Research, New Delhi, India

ARTICLE INFO

Article history:
Received 24 June 2015
Accepted 8 August 2015
Available online 9 October 2015

The availability of Xpert MTB/RIF has greatly influenced the diagnosis and management of people with pulmonary tuberculosis. This molecular test identifies *Mycobacterium tuberculosis* DNA in sputum, provides information on the susceptibility of the bacterium to rifampicin, and gives results in less than two hours. Notwithstanding the major advantage of reliability and speed, it is an expensive test and affordability is a major concern. Though companies in addition to *Cepheid* are developing similar machines, the costs of these tests are still quite high, over $10, despite being subsidized. Though research is in progress to develop new diagnostics and address some of the drawbacks of Xpert, it is unlikely that an equally good test at an affordable price would become available soon. The question, therefore, is how do we maximize the benefits of existing test.

In countries like India, where the burden of TB is high, the criteria for identifying individuals who are suspected to have pulmonary tuberculosis and are advised to undergo a diagnostic test are nonspecific. Since most people suspected of having TB do not have TB, it is not cost effective to have costly confirmatory tests run on their sputum samples. A policy to have a strategy to use a triaging would help in judicious use of expensive confirmatory tests.

Can we rule out TB before subjecting an individual to a more expensive test?

Yes, by using a triage strategy.

Triage is a process of sorting affected people into groups based on their need for or likely benefit from immediate medical treatment. Triage has been conventionally used in battlefields, emergency rooms, or in disaster sites when limited medical resources must be allocated to the most in need. If an inexpensive triage test is positive, only then would a more expensive and more specific confirmatory test be done. If the triage test is negative, it would mean excluding the disease. The sensitivity of the triage test would be maximized at the expense of specificity, while specificity is a trade-off with the cost. Triaging in tuberculosis is an exciting and relatively new preposition and has attracted considerable interest.

The importance of community-based triage test for identifying people suspected of having TB was highlighted in a report of consensus achieved at a meeting, convened by WHO on high-priority target product profiles for new tuberculosis diagnostics.[1] The report has identified a triage test as one of the four high-priority target product profiles to guide the development of new diagnostics for tuberculosis. Ideally,

* *Correspondence to*: B-95, Gulmohar Park, New Delhi 110 049, India. Tel.: +91 98685 02018.
E-mail address: drlalitkant@gmail.com
http://dx.doi.org/10.1016/j.ijtb.2015.09.005

"a triage test needs to be a simple low-cost test that can be used by first-contact providers in the community (such as community health workers) to rule out TB (that is, to identify people who are triage-test negative) and direct individuals who require further evaluation (that is, those who are triage-test positive) to a confirmatory test (such as the Xpert MTB/RIF assay or similar molecular test). Triage testing could take place at the same level of care as confirmatory testing, especially in settings that see a large number of patients (such as outpatient clinics), but typically a triage test is conceived to be used at lower levels of care..."

It lists out six key performance and operational characteristics of the triage test. One of the requirements is that a triage test should optimally have a sensitivity of more than 95% (minimum >90%) and specificity of >80% (minimum >70%) as compared with the confirmatory test for pulmonary tuberculosis. The cost of the triage test should ideally be <US$1, and in any case should not be more than US$2.

A modeling exercise has been done to inform the selection and development of particular diagnostics as a triage test by exploring combinations of sensitivity, specificity, and cost at which a hypothetical triage test will improve affordability of the Xpert assay. In a decision analytical model parameterized for three countries including India, the investigators compared a diagnostic algorithm in which a cohort of patients with presumptive TB received Xpert to a triage algorithm whereby only those with a positive triage test were tested by Xpert. A triage test with sensitivity equal to Xpert, 75% specificity, and costs of US$5 per patient tested would be able to reduce total diagnostic costs by almost a third in the Indian settings. They concluded that a triage test strategy could potentially improve the affordability of Xpert for TB diagnosis, particularly in low-income countries and with enhanced case-finding.[2]

As of today, no triage test exists for tuberculosis. But, there are several in the pipeline. Some are based on detection of biologic markers in body fluids (for example C-reactive proteins, procalcitonin, neoptin, CXCL10) while others are new technologies.[3] Some or most of them do not meet the specifications of a triage test, but may, however, be modified in future into a triage test.

The test that come closest to a triage test are chest X-ray (CXR).

CXR has been used to detect abnormalities in lung to diagnose tuberculosis. Several technological hurdles have hindered the widespread application of CXRs in resource-limited settings. It is difficult to have data on the sensitivity and specificity for CXR due to variations in study populations and methods used; it is generally agreed that chest X-rays have relatively high sensitivity for TB (80–95%), but modest specificity (70–75%), as several other lung diseases can cause similar X-ray abnormalities. Therefore, chest X-ray is not a bad triage tool, and can identify those who require confirmatory testing. One major problem with CXR remains: an expert needs to interpret the images. But the situation is changing.

The advances in digital technology have made chest X-rays cheaper and easier to use because films and chemicals are no longer needed and are more reliable because automatic exposure control largely avoids unreadable images. Today, CXR is becoming more accessible in remote settings due to technological advances. With a portable digital X-ray, even remote groups can be screened at low cost, as the incremental costs of digital X-ray are very low. Digitalization has also made it possible to score chest radiographs automatically using computer-aided diagnosis software programs. It has decreased the dependency on radiologist or a physician to read an X-ray.

Computer-aided diagnosis (CAD) is a relatively young technology. It employs artificial intelligence, pattern recognition, and machine learning techniques to automatically identify radiological markers of abnormality. Commercial CAD software platforms are now available and routinely used in resource-rich settings for radiological assessment of digital/computed X-ray/MRI/CT scans for breast/lung/prostrate/colon cancers, coronary artery disease, congenital heart disease, and nuclear medicine. However, development of CAD for TB has been a recent phenomenon.

Computer aided diagnosis (CAD) software can immediately analyze these digital images and give a probability percentage normal vs. abnormal consistent with TB. The digital image can be interpreted on the spot within seconds to recognize image patterns consistent with TB.

Presently there is only one commercial Computer Aided Diagnosis for pulmonary tuberculosis (CAD4TB) detection platform available globally from Delft Imaging Systems. The software can run only on digital X-ray system made by a specific manufacturer. It is learnt that in India, AdvenioTecnosys has also developed a CXR lung abnormality detection CAD algorithm. The Indian company has attempted to improve upon existing system by addressing its shortcomings. It aims to provide a CAD assisted detection of TB from digital X-rays with ~90% sensitivity and ~80% specificity. The platform is now ready for validation.

The first CAD4TB prototype software was developed and field tested in 2010. As more experience pours in, the software is being constantly improved and several versions have been developed since then. The objective of the developmental research is to achieve an electronic TB screening capability with a sensitivity of 90% and a specificity of 80%. Within just two minutes from exposure, the software automatically analyses chest X-rays, detects abnormalities, and indicates the likelihood of active TB. In various studies, CAD4TB has been shown to be as accurate as trained human readers to detect abnormalities consistent with TB, confirming that CAD can be used cost effectively as a triage tool for Xpert eligible subjects.

CAD4TB was evaluated on chest radiographs of patients with symptoms suggestive of pulmonary tuberculosis enrolled in two cohort studies in Tanzania. The system accurately distinguished between the chest radiographs of culture-positive TB cases and controls.[4]

A prospective study to determine the sensitivity and specificity of a CAD4TB program for scoring chest X-rays of presumptive tuberculosis (TB) patients compared to Xpert MTB/RIF (Xpert) was carried out in Lusaka, Zambia. The study showed that the CAD program had high sensitivity but low specificity. The investigators concluded that the use of CAD with digital CXR has the potential to increase the use and availability of chest radiography in screening for TB where trained human resources are scarce.[5]

Triage tests open a new window of opportunity to maximize the usage of expensive confirmatory tests for tuberculosis. These tests would be most useful for high-burden resource-constrained

countries like India. In view of the advantages it offers, use of digital X-rays is becoming common in the private sector. The Central and the State Governments are also floating tenders for purchase of digital X-ray machines. Hopefully, computer-aided diagnosis platforms developed abroad and/or in India would be soon available at competitive prices. The RNTCP should review the strategy of using triage test(s) keeping in mind the potential benefits it offers in terms of reduction in costs for the program and the workload of health-care staff, and the increase in the number of patients who would be identified as having TB and put on treatment. It should also view the advantages that the technology offers in light of shortage of radiologists, and physicians to interpret an X-ray. Simultaneously, research agencies should put into action programs for validation of available systems in Indian conditions, look into the cost-effectiveness, and operational and ethical aspects of the use of CAD in India.

Conflicts of interest

The author had reviewed a proposal from AdvenioTechnosys for funding from the Bill & Melinda Gates Foundation.

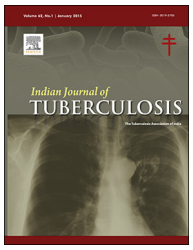
REFERENCES

1. WHO. *High-priority target product profiles for new tuberculosis diagnostics: report of a consensus meeting*. Geneva: World Health Organization; 2014:19–25.
2. van'tHoog AH, Cobelens F, Vassall A, et al. Optimal triage test characteristics to improve the cost-effectiveness of the Xpert MTB/RIF assay for TB diagnosis: a decision analysis. *PLoS ONE*. 2013;8(12):e82786. http://dx.doi.org/10.1371/journal.pone.0082786.
3. Garcia-Basteiro AL, Coblelens F. Triage tests: a new priority for tuberculosis diagnostics. *Lancet Respir Med*. 2015;3:177–178.
4. Breuninger M, van Ginneken B, Philipsen RHH, et al. Diagnostic accuracy of computer-aided detection of pulmonary tuberculosis in chest radiographs: a validation study from sub-Saharan Africa. *PLoS ONE*. 2014;9(9):e106381. http://dx.doi.org/10.1371/journal.pone.0106381.
5. Muyoyeta M, Maduskar P, Moyo M, et al. The sensitivity and specificity of using a computer aided diagnosis program for automatically scoring chest X-rays of presumptive TB patients compared with Xpert MTB/RIF in Lusaka Zambia. *PLoS ONE*. 2014;9(4):e93757. http://dx.doi.org/10.1371/journal.pone.0093757.

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: http://www.journals.elsevier.com/indian-journal-of-tuberculosis/



Continuing Medical Education

Evolving immunological frontiers in tuberculosis

Mandakolathur R. Murali [a,*], *Pudupakkam K. Vedanthan* [b]

[a] *Director of Clinical Immunology Lab and Physician Division of Allergy, Clinical Massachusetts General Hospital, Harvard Medical School, Departments of Medicine and Pathology, Clinical Immunology Laboratory, Bulfinch, 55 Fruit Street, Boston, MA 02114, USA*

[b] *University of Colorado, Denver, CO, USA*

ARTICLE INFO

Article history:
Available online 4 November 2015

Understanding of the pathogenesis of tuberculosis began with the work of Rene Theophile Laennec at the beginning of the 19th century and was advanced further by the demonstration of the transmissibility of *Mycobacterium tuberculosis* infection by Jean-Antoine Villemin in 1865 and the identification of the tubercle bacillus as the etiologic agent by Robert Koch in 1882.[1] Epidemiological data from the WHO show that in 2013, 9 million people fell ill with Tuberculosis (TB) and 1.5 million died from the disease, with 95% of deaths occurring in low- and middle-income countries. TB is the second greatest killer worldwide due to a single infectious agent, being surpassed by only HIV/AIDS.[2]

The natural history of TB begins with the inhalation of aerosol droplets of *Mycobacterium tuberculosis (MTb)* by the human host. The resulting innate as well as adaptive immune response, between the host and (*MTb*), leads to one of four possible outcomes[3] (see Fig. 1a and b):

(a) immediate or early clearance,
(b) progressive primary infection,
(c) latent infection, and
(d) breakdown of latent infection leading to reactivation disease.

(a) Immediate or early clearance is orchestrated by innate immune mechanisms. The cell wall of *MTb* is endowed with glycolipids, lipoarabinomannan, lipoproteins, etc., which serve as pathogen-associated molecular patterns (PAMPs) and they bind to pattern recognition receptors (PRRs) found on the surface or in the cytosol of innate cells – the alveolar macrophages being the primary target and possibly the epithelial cells of the lung also. The PRRs include the transmembrane Toll-like receptors (TLRs), the cytosolic nucleotide-binding oligomerization domain (NOD)-like receptors, and C-type lectins. These PRRs bind to the PAMPs expressed by *Mtb*, and initiate pro-inflammatory cytokine signals that influence mycobacterial killing and clearance. Specifically, TLR2 binds lipoarabinomannan, and as a dimer with TLR6 binds *MTb* lipoprotein. These signals are transmitted via MyD88 pathways leading to transcription of nuclear transcription factor-KB (NF-κB) culminating in production of inflammatory cytokine secretion, particularly tumor necrosis factor-α (TNF-α).[4,5] TNF-α is a very important and potent cytokine involved in *MTb* elimination. TLR 4 activation by lipoproteins leads to interleukin 1β (IL-1β) production. TLR8 and TLR9 are endosomally located and so are able to detect the nucleic acids of *MTb* derived from intraphagosomal degradation of the *MTb*. NOD-like receptor activation also recruits the inflammasome pathway, activates caspase-1, and generates active IL-1β. The clinical importance of this pathway is underscored by the fact that polymorphisms of this pathway, specifically caspase recruitment domain – containing protein

* *Corresponding author*. Tel.: +1 617 726 3860/781 229 7727; fax: +1 617 724 3847.
E-mail address: Murali50@aol.com (M.R. Murali).

http://dx.doi.org/10.1016/j.ijtb.2015.09.009

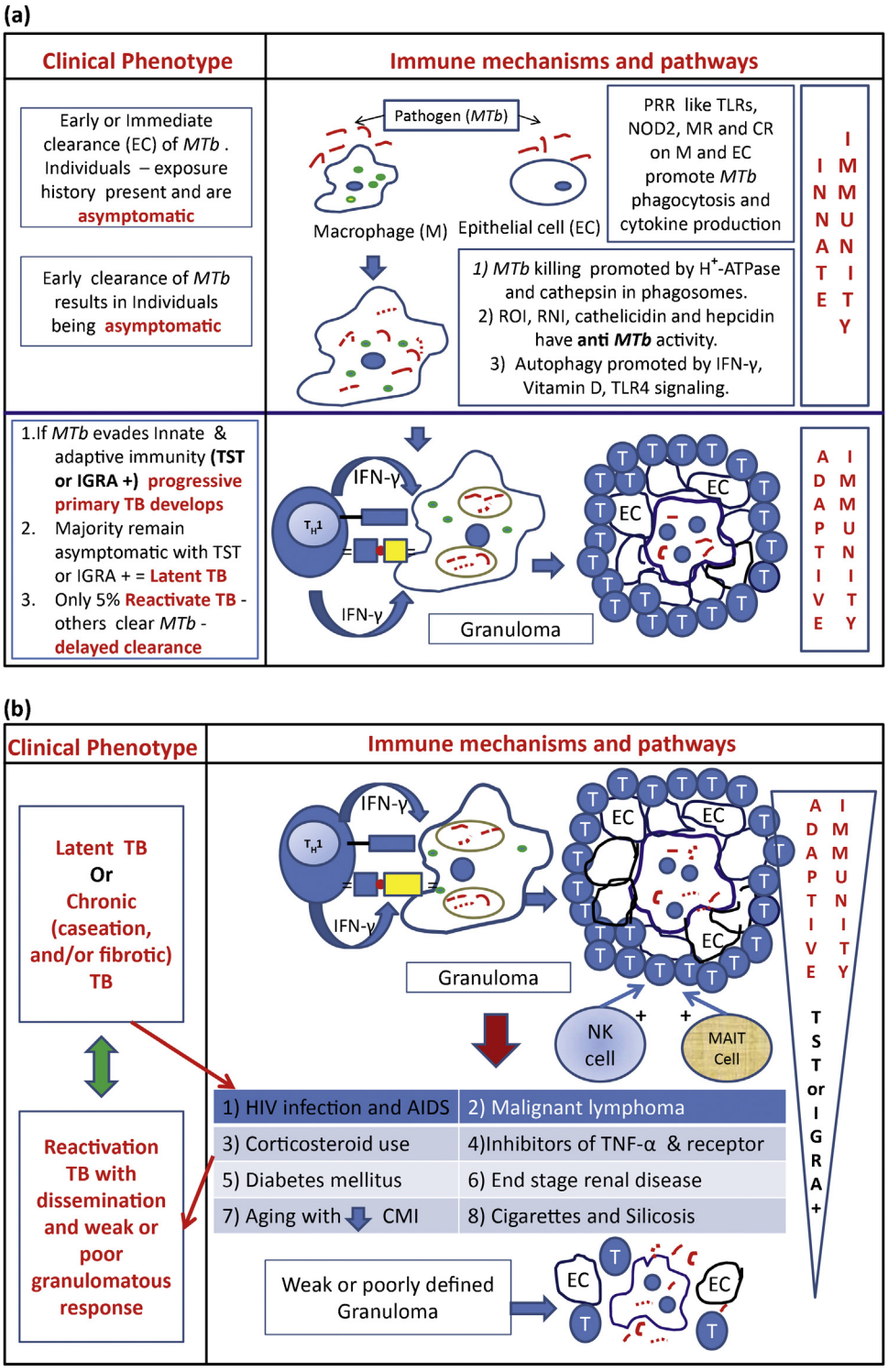


Fig. 1 – (a) Both, innate and adaptive immune mechanisms, are operative in humans after inhalation of *MTb*. At this stage, infection is primarily of alveolar macrophages and subjects are asymptomatic. Activation of macrophages is important for early clearance (EC), through recognition of *MTb* via surface, cytosolic, or phagosomal PRRs. This promotes killing of intracellular *MTb* by phagosomal acidification, hydrolytic enzymes, and generation of reactive nitrogen and oxygen intermediates. Also, antimicrobial peptides and autophagy promote mycobacterial killing and both are induced by vitamin D. Alternatively, infection is favored if the macrophage's initial interaction with *MTb* is via ligation of the mannose receptor (MR). This promotes uptake of *MTb* without immune recognition and inhibition of phagolysosomal fusion. Infected macrophages undergo apoptosis and express adenosine triphosphate and phosphatidyl serine. This attracts monocytes and neutrophils that engulf the infected cell and deploy oxidative killing mechanisms to achieve clearance. Activated neutrophils secrete antimicrobial peptides cathelicidin, human neutrophil peptides, and Lipocalin 2 to kill infected monocytes. Sustained

8, are associated with risk of *MTb* in HIV-infected subjects.[6] On the other hand, when *MTb* is recognized by mannose receptor (MR) as well as dendritic cell-specific intracellular adhesion molecule 3-grabbing nonintegrin called (DC-SIGN), an anti-inflammatory signal, like Type I interferon, is generated that impairs *MTb* killing and favors mycobacterial persistence. The resulting balance between these two opposing pathways determines the net outcome – early clearance promoted by TNF-α and IL-1β versus Type 1 IFN that leads to *MTb* persistence and disease exacerbation.[7]

Mycobacterial killing is a vital step in elimination or decreasing the *MTb* reservoir. *MTb* killing is promoted by H^+-ATPase and cathepsin produced in the phagolysosomes. Reactive oxygen intermediates (ROI), derived from NADPH oxidase, and reactive nitrogen intermediates (RNI), derived from nitric oxide synthetase (NOS), are lethal to *MTb*. There is epidemiologic evidence supporting the importance of RNIs in TB control. Freidman and colleagues found that a common drug-susceptible strain of *MTb*, found in late 1990s in New York City (C strain), was resistant to RNI generated in vitro and was associated with injection drug use.[8] Ehrt and associates used this strain to identify a novel gene called noxR1.[9] Expression of this gene in nonpathogenic strains of *E. coli* or *M. smegmatis* resulted in increased resistance to RNIs and ROSs in vitro. Cell wall constituents from virulent strains of *MTb* inhibit phagolysosome fusion and evade killing. Macrophages overcome this inhibition by deploying autophagosomes that engulf phagosomes and force lysosomal fusion.[10] Autophagy, a process in which dead cell organelles are disposed or recycled, limits host tissue damage and is promoted by IFN-λ and Vitamin D.[10] Macrophages infected with *MTb* produce cathelicidin and hepcidin, which have direct anti-*MTb* killing activity.[10] Further, apoptotic macrophages express ATP and phosphatidyl serine to promote its efferocytosis by other phagocytes that kill the bacterium.[11] This is analogous to ''burying the dead'' – in this case the *MTb*. Virulent strains evade apoptosis and induce necrosis. This prevents repair of the plasma membrane. The resulting disruption of macrophage membrane favors *MTb* escape, *MTb* overgrowth, and escalation of infection.[12]

Besides macrophages, the phagocytic neutrophil either spontaneously or when augmented by TNF-α can kill *MTb*. Killing is associated with increased serum levels of neutrophil antimicrobial peptides, such as cathelicidin, lipocalcin, and neutrophil peptides 1 and 3.[13]

NK cells, γδ T cells, and mucosa-associated invariant T (MAIT) cells express germ-line encoded PRRs that endow them to function as innate immune cells. NK cells produce IFN-γ and IL-22, which promote *MTb* killing and macrophage apoptosis.[10] MAIT cells respond rapidly to danger signals and provide an early innate source of IFN-γ, which enhances macrophage activation. γδ T cells are present in alveoli and recognize mycobacterial phosphoantigens expressed on infected macrophage membranes.[10] They are a source of cytotoxic granules, IFN-γ and TNF-α. These cells synergize with CD8 cells in *MTb* killing.

(b) Progressive primary infection develops in about 5–10% of the subjects infected with *MTb*. In about less than half of these, wherein innate immunity of the host fails to eliminate infection, the bacilli proliferate inside the macrophages, escape the phagolysosomal killing, and migrate into lung tissue. If the macrophage kills and processes the *MTb* antigens, it then presents these antigenic determinants in an MHC class II dependent manner to CD4+ T cells along with IL-1 and IL-12, and these T cells make IL-2 and IFN-γ. This represents the adaptive immune response. IL-2 activates the responding CD4+T cells as well as CD8+ cells. IFN-γ activates macrophages and monocytes to become epithelioid cells and also multinucleated giant cells. Thus, a granuloma is generated around the dying lipid-laden *MTb* in a process called caseation necrosis, and decorated by a granulomatous cellular collection of multinucleated giant cells and epithelioid cells, and walled off by activated T cells, their cytokines including TGF-β that activates fibroblasts.[14] This is called a tubercle, and when host immunity excels, the *MTb* is entombed by calcification of the tubercle. If the immune response fails, the *MTb* spreads to adjoining pulmonary parenchyma and regional nodes to form the Ghon complex. Bacteremia results in dissemination of TB to other organs and presents as active TB pneumonia, military TB, and even meningeal TB. This is called progressive primary infection.[15]

(c) Latent infection. As noted above, the innate and adaptive immune responses, more often than not, result in an asymptomatic latent TB infection, which is defined as a state of persistent bacterial viability, and no evidence of clinically manifested active TB. As this stage, latent TB is diagnosed by recalling *MTb*-specific T cell immune responses to in vivo tuberculin skin test (TST) or in vitro stimulation of peripheral blood lympho-mononuclear cells (PBMC) by *MTb* antigens. The read out of this test is by the release of INF-γ from *MTb*-specific T cells – called the interferon gamma release assays (IGRAs). TST is inexpensive and widely used but has poor specificity in subjects vaccinated with bacilli Calmette-Guerin (BCG) and in those who have nontuberculosis

infection is most likely when infected macrophages undergo necrotic cell death. The disruption of the macrophage membrane facilitates mycobacterial outgrowth, so newly recruited monocytes are infected and logarithmic growth ensues. Adaptive immunity results from *MTb* antigen presentation by macrophages to CD4+ T cells and the resulting cytokine milieu activates macrophages to become multinucleated giant cells, surrounded by epithelioid cells and walled off by T cells and fibroblasts to form a granuloma or tubercle. IFN-γ and TNF-α are essential in this phase of adaptive immunity. Subjects at this stage may or may not be positive for TST or IGRAs, and if asymptomatic, they are deemed as having latent infection. Breakdown of this immune response leads to progressive primary TB. Only 5% reactivate their *MTb* infection to manifest TB. Elimination of *MTb* at this stage is called delayed clearance. NK cells and MAIT secrete γ-interferon. (b) A robust granulomatous response contains the *MTb* infection and subjects are asymptomatic with a positive TST or IGRAs – a hallmark of adaptive immune sensitization. A derangement in this immune homeostasis, such as in HIV infection, immunosuppressive drugs, malignancy, etc., results in a breakdown of immune barriers and reactivation of TB results, which has a possibility of dissemination to many organs. The ensuing dysregulated cytokine contributes to the systemic features, such as fever, cachexia, etc.

mycobacteria due to cross-reactivity among these and *MTb*. It has poor sensitivity in those who are immunocompromised.[16] Accurate reading of the induration and interobserver errors make TST less reliable. The specificity of IGRAs for *MTb* is higher than TST, as the antigens used for stimulating the PBMC, such as early secretory antigenic target 6 (ESAT-6) and culture filtrate protein (CFP-10), are not found in BCG and most nontuberculosis mycobacteria. False conversions between positive to negative and vice versa are more common in IGRAs than TST. The cost and need for a laboratory make it less useful in epidemiological studies in developing nations of the world.[16] Immune mechanisms underlying the latent infection, development of reliable biomarkers, optimizing antimycobacterial therapy, and boosting beneficial immune containment of *MTb* by vaccines are opportunities awaiting basic and clinical investigators.

(d) Reactivation of latent infection results when either the virulence of the *MTb* is profound or there is a breakdown of immune responses. The collapse of innate and adaptive immune responses, both cellular and cytokine network, is often due to risk factors, such as HIV, lymphoma, use of TNF-α antagonists, sustained or high-dose corticosteroid administration, diabetes mellitus, chronic renal failure, cigarette smoking, and silicosis. The mechanisms underlying this failure of protective immunity in active TB has been reviewed recently using blood transcriptional signature.[7] The signature of active TB is dominated by over expression of interferon-inducible genes (consisting of both Type I and Type II interferon signaling), myeloid genes, and inflammatory genes. There is also downregulation of genes influencing T and B cell functions. It has been shown that type I IFN induces the suppressive cytokine IL-10 and IL-1RA, as well as iNOS. IFN 1 (IFN α/β) also inhibits production of the important proinflammatory and protective cytokines IL-12 and TNF-α. Further, the type 1 IFN blocks the ability of IFN-γ (a type II-IFN) to activate macrophages and thus control mycobacterial growth or produce the protective cytokine IL-12. Thus, the balance of induction of these two cytokines dictates the outcome of infection with *MTb*.[17] This blood signature of TB correlates with the extent of radiographic disease and is diminished by effective treatment suggesting the possibility of new improved strategies to evaluate diagnostic assays, therapeutic modalities, and monitoring of disease activity.[7]

In conclusion, it is to be noted that the majority of individuals in the general population who become infected with *MTb* never develop clinical disease. This is a testimony to the effective evolution of the innate and adaptive immune responses of the human host in controlling *MTb* infection. The latent phase represents a dynamic reservoir of infection and at the moment only TST and IGRAs can detect this cellular phase of immunity, as there are no characteristic clinical features. Factors that adversely affect the immune system contribute to the escalation of latent TB infection to active disease. These risk factors need recognition and treatment in a timely manner to decrease the global incidence of *MTb* infection. Recent advances in blood transcriptomal signatures have shed light on this dynamic balance of the immune system.

The battle during mycobacterial evolution, including the acquisition of multidrug resistant genes that thwart the efficacy of therapeutic agents and a better understanding of the immunogenetic diversity of the human host, holds promise for development of better drugs and vaccines and ushers in a new era of TB prevention and treatment.

Conflicts of interest

The authors have none to declare.

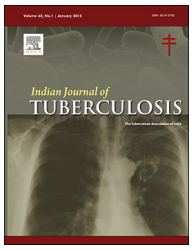
REFERENCES

1. Daniel TM. The history of tuberculosis. *Resp Med*. 2006;100:1862–1870.
2. WHO. Tuberculosis (Internet). Geneva: World Health Organization. Available from: http://www.who.int/mediacenter/factsheets/fs104/en Accessed 12.3.13.
3. O'Garra A, Redford PS, McNab FW, Bloom CI, Wilkinson RJ, Berry MP. The immune response in tuberculosis. *Annu Rev Immunol*. 2013;31:475–527.
4. Thoma-Uszynski S, Stenger S, Takeuchi O, et al. Induction of direct antimicrobial activity through mammalian Toll-like receptors. *Science*. 2001;291:1544–1547.
5. Underhill DM, Ozinsky A, Smith KD, Aderem A. Toll-like receptor-2 mediates mycobacteria-induced proinflammatory signaling in macrophages. *Proc Natl Acad Sci U S A*. 1999;96:14459–14463.
6. Pontillo A, Carvalho MS, Kamada AJ, et al. Susceptibility to *Mycobacterium tuberculosis* infection in HIV-positive patients is associated with CARD8 genetic variant. *J Acquir Immune Defic Syndr*. 2013;63:147–151.
7. Cliff JM, Kaufmann SHE, McShane H, Helden PV, O'Garra A. The human immune response to tuberculosis and its treatment: a view from the blood. *Immunol Rev*. 2015;264:88–102.
8. Friedman CR, Quinn GC, Kreiswirth BN, et al. Widespread dissemination of a drug-susceptible strain on *Mycobacterium tuberculosis*. *J Infect Dis*. 1997;176:478–484.
9. Ehrt S, Shiloh MU, Ruan J, et al. A novel antioxidant gene from *Mycobacterium tuberculosis*. *J Exp Med*. 1997;186:1885–1895.
10. Verrall AJ, Netea MG, Alisjahbana B, et al. Early clearance of *Mycobacterium tuberculosis*: a new frontier in prevention. *Immunology*. 2014;141:506–513.
11. Martin CJ, Booty MG, Rosebrock TR, et al. Efferocytosis is an innate antibacterial mechanism. *Cell Host Microbe*. 2012;12:289–300.
12. Divangahi M, Chen M, Gan H, et al. *Mycobacterium tuberculosis* evades macrophage defenses by inhibiting plasma membrane repair. *Nat Immunol*. 2009;10:899–906.
13. Martineau AR, Newton SM, Wilkinson KA, et al. Neutrophil-mediated innate immune resistance to mycobacteria. *J Clin Invest*. 2007;117:1988–1994.
14. Orme IM, Cooper AM. Cytokine/chemokine cascades in immunity to tuberculosis. *Immunol Today*. 1999;20:307–312.
15. Modlin RL, Bloom BR. TB or not TB: this is no longer the question. *Sci Transl Med*. 2013;5:. 213sr6.
16. Getahun H, Mateelli A, Chaisson RE, Raviglione M. Latent *Mycobacterium tuberculosis* infection. *N Engl J Med*. 2015;372:2127–2135.
17. Teles RM, Graeber TG, Krutzik SR, et al. Type I interferon suppresses type II interferon-triggered human anti-mycobacterial responses. *Science*. 2013;339:1448–1453.

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: http://www.journals.elsevier.com/indian-journal-of-tuberculosis/



Continuing Medical Education

Medical thoracoscopy in the management of tuberculous pleural effusion☆

B.N.B.M. Prasad

Director, General Hospital Services (AF), M Block, New Delhi, 110 001, India

ARTICLE INFO

Article history:
Available online 4 November 2015

1. Introduction

Exudative pleural effusion is common in clinical practice and tuberculosis continues to be an important cause in many parts of the world, including India, where it is endemic. India, with about 40% of her total population of over 1.2 billion already infected with TB bacillus, has the highest tuberculosis burden in the world and accounts for 25% of global incidence.[1,2] In many endemic parts of the world, more than 25% of all exudative effusions are due to tuberculosis.[3–7]

In recent years, among western population, the incidence of tuberculous pleural effusion has decreased substantially. On the other hand, malignant pleural effusions are much more common. In USA, around 1000 cases are reported annually as against 200,000 cases for malignant pleural effusion.[8] However, the disease may be under-reported in view of frequently negative mycobacterial confirmation.

Pleural involvement by tuberculosis usually occurs following a primary infection or may be due to reactivation of an old infection. In USA, 3–5% of tuberculosis patients have TB pleuritis.[8,9] Much higher incidence of pleural involvement – 11–20% among patients with thoracic TB and still higher – 23–38% in those with concomitant HIV infection have been reported from some African countries.[10–12]

The management of tuberculous pleural effusion is challenging and has gained critical importance in the present context of HIV epidemic and multidrug/total drug resistance. Tuberculosis of the pleura is considered to be one among the severe forms of extra-pulmonary tuberculosis. Not only there is resurgence of tuberculous pleural effusion in HIV/AIDS with incidence varying from 15% to 90%,[9] but also there are problems in establishing diagnosis and treating as the disease can be severe, atypical in presentation and associated with opportunistic infection and drug resistance. Tuberculosis of pleura often affects young adults in developing countries while in industrial countries, and also following reactivation, patients are much older.[13–15] The disease presents with sub-acute illness of fever, weight loss, pleuritic chest pain and dry cough. Onset can be acute with clinical features similar to that of bacterial para-pneumonic pleurisy, which is also the most important differential diagnosis.[16] The duration of illness is longer, incidence of chest pain is low, systemic features are much more pronounced, associated lung involvement is likely and so also is pleural fluid positivity for AFB among those with HIV infection.[17,18] Pleural effusion is commonly mild to moderate in size, and in some massive, often unilateral and associated with parenchymal infiltrates in approximately 20–40% of cases.[19,20] Tuberculin skin testing helps in diagnosis with reported tuberculin positivity of 66.5% among cases of tuberculous pleuritis.[12] It is to be noted that negative test does not rule out tuberculosis and more than half of the cases may be tuberculin negative.[21] Tubercular pleural fluid is an exudate with very high lymphocyte count (usually more than 50%), protein level more than 5 g/dL, ADA more than 40 U/L and interferon-Gamma more than 3.7 IU/mL.[9,19,22–25] Transient

☆ Dr. S.N. Tripathy Memorial Oration delivered at the 69th National Conference on Tuberculosis and Chest Diseases held in Mumbai on 6th and 7th February 2015.

E-mail address: shashirekhak@rediffmail.com.

http://dx.doi.org/10.1016/j.ijtb.2015.09.010

pleural fluid neutrophilia may be observed in acute cases and in early stages of the disease.[26] Mesothelial cells in significant numbers may be observed in pleural fluid in those with HIV co-infection.[27] Excessive LDH elevation and low glucose and pH values in pleural fluid are only suggestive of tuberculosis and are nonspecific.[28] Polymerase chain reaction (PCR) can be helpful for pleural space infections, although its role is limited by high false-positive rates.[29] MTB gene probes, such as the AMPLICOR MTB®, AMTDT® or AccuProbe® sets targeting IS 6110 DNA or 16S-rRNA sequence, are commercially available and offer an optimum specificity of about 100% and overall sensitivities up to 80–90%, in both fluid and tissue samples. However, in pauci-bacillary culture negative pleurisy, limited sensitivity has been observed.[30] Smears and cultures of sputum for mycobacteria should be done in suspected tuberculous pleural effusion cases, even in those with no lung infiltrates on chest radiography. In one study, induced sputum was found positive for AFB in 55% of cases having no parenchymal infiltrates.[31] The reported positivity for AFB by smear in pleural fluid is less than 20% especially in nonimmunosuppressed patients since TB pleuritis is a type IV hypersensitivity reaction to mycobacterial proteins.[25,32] By using BACTEC system for pleural fluid mycobacterial culture, positive culture has been obtained in 75% of cases with HIV co-infection.[33] In equivocal cases, needle biopsy or thoracoscopic biopsy is required to demonstrate characteristic caseating granuloma for establishing the diagnosis of tuberculous pleural effusion.[34] Closed pleural biopsy may not confirm diagnosis in more than half of the cases, and in such cases, thoracoscopic evaluation to determine the cause of exudative effusion needs serious consideration.

2. Medical thoracoscopy

2.1. *History and evolution*

Though the first thoracoscopy was performed in 1865 by Francis-Richard Cruise in Ireland,[35] the credit for introducing this technique in clinical practice in the year 1910 and subsequently popularising it goes to the famous Swedish Physician – Hans-Christian Jacobaeus, who is universally acclaimed as the father of thoracoscopy.[36] At that time, one of the widely practiced therapy for pulmonary tuberculosis was the creation of artificial pneumothorax to collapse the lung, and Jacobaeus used his new technique of pleuroscopy termed ''Jacobaeus operation'' (that he performed using cystoscope with two different points of entry under local anaesthesia) for the diagnosis of tuberculous pleural effusions and lysis of adhesions between the parietal and visceral pleura (that prevented a complete artificial pneumothorax) by elctrocautery.[37] This procedure after its advent was used for the next 40 years with subsequent sharp decline in its use in 1950s following the introduction of anti-tubercular drugs for the therapy and pleural needle biopsy for the diagnosis of pleural tuberculosis.[38] During the 1960s, there was a slow revival of the technique in Europe with a gradual increase in its utilisation over the next three decades.[39–45] Following the advent of laparoscopic cholecystectomy in the early 1990s, thoracic surgeons developed surgical thoracoscopy subsequently coined as ''Video-Assisted Thoracic Surgery'' or ''VATS'' for surgical management of various intra-thoracic conditions.[46–48] Medical thoracoscopy that was mostly confined to a few centres in Europe during the last century has now found its rightful place in many parts of English speaking and developing countries, and several pioneers in the field have contributed for this substantial growth.[42–44,49–52] Thanks to rapid strides in imaging and endoscopic technology, newer generations of user friendly rigid/semi-flexible thoracoscopes with sophisticated instruments similar to those used in bronchoscopy[53–57] are now available.

Unlike VATS, medical thoracoscopy, also known by the old term pleuroscopy, is a less invasive and less expensive endoscopic procedure that is performed by a Pulmonologist under local anaesthesia and conscious sedation using simple instruments through a single or double port. It has now become an excellent tool for the diagnostic and therapeutic exploration of pleural cavity in exudative pleural effusions of undetermined aetiology when less invasive procedures have failed.[34] Due to its wider application, thoracoscopy has emerged as the commonest endoscopic procedure in Thoracic Medicine after bronchoscopy that is performed by the Pulmonologist. It is essential that the Pulmonologist who practice medical thoracoscopy should have adequate training and competence.[58–60]

2.2. *Indications*

In tuberculous pleural effusion, medical thoracoscopy is indicated to confirm the diagnosis by pleural biopsy when other less invasive procedures are nondiagnostic. It can be performed for the lysis of pleural adhesions and loculations that hinder complete evacuation of fluid/air and expansion of lung.[34]

2.3. *Contraindications*

Obliteration of pleural space due to pleural thickening or multiple adhesions preventing the safe insertion of thoracoscope/pleuroscope without damaging lung or other organs is a major contraindication for the procedure. Recent myocardial infarction, cardiac arrhythmias, end-stage pulmonary fibrosis, unstable cardiovascular status, coagulation disorder, uncooperative patient, persistent cough, respiratory failure and renal dysfunction are some of the contraindications.[34]

2.4. *Preprocedure evaluation*

While selecting the case for medical thoracoscopy, a comprehensive evaluation by detailed medical history, physical examination, imaging (by chest radiography, pleural ultrasonography or chest computed tomography), pulmonary function testing, electrocardiogram (ECG), complete blood counts, coagulation studies, blood gas analysis and blood chemistry including renal and liver function tests is essential.[49,61–67]

2.5. *Equipments*

The equipments required for the performance of medical thoracoscopy in pleural effusion include a pleural needle,

trocar (obturator and a cannula; an additional insulated trocar for the second port), thoracoscope/pleuroscope: a direct-viewing and angle-viewing optical telescope, an optical biopsy forceps, unipolar coagulation forceps, light source, video system, aspiration system and chest tubes,[34,67] besides those for monitoring and emergency care.

The use of either rigid or semirigid flexible thoracoscope has some specific advantages,[34,68] although the final outcome and the preference for a particular type of thoracoscope is based on the availability of resources and confidence and experience of the operator. Rigid thoracoscope has advantages of excellent vision, obtaining large biopsy samples via a single port of entry, ease of obtaining biopsy from harder lesions, easy orientation inside the pleural cavity and better control of complications such as haemorrhage and air leak. The rigid instruments are easy to maintain, less expensive, durable and robust. The Pulmonologist who is otherwise apt in performing fibreoptic bronchoscopy prefers semirigid flexible pleuroscope that can be used by using parts of the bronchoscopy equipment, e.g., the light source, processor and monitor, thereby reducing the acquisition costs. Clear optical field for better visualisation can be obtained by allowing concurrent suctioning. Flexible tip of endoscope permits better manoeuvring in different directions around adhesions. Its flexible tip facilitates the homogeneous insufflations of talc (via a catheter), introduced through the working channel, into all areas of the parietal and visceral pleura. The inherent disadvantages of flexible instruments include their fragility, specific sterilisation requirements, high maintenance costs and inability to obtain large size biopsies. Ideally, both types of endoscopes can be used as complementary to each other in a given situation.

2.6. Procedure[34,67]

Patient is made to lie comfortably on the endoscopy table usually in the lateral decubitus position with the healthy side up. In order to widen the intercostal space so as to create more space for manipulation of instruments without discomfort to the patient, a round bolster can be placed underneath the thorax and upper arm held over the head and placed on metal cradle.

Medical thoracoscopy is performed either with a single or a double port. In the single port method usually 9-mm rigid thoracoscope or 7-mm semirigid/semi-flexible pleuroscope with a working channel for accessory instruments and optical biopsy forceps is introduced into the pleural cavity. Majority of tuberculous pleural effusions can be managed by this method. Occasionally, double port method is required wherein one port is utilised for the examination telescope and the other for accessory instruments, including the biopsy forceps, and is usually performed with conscious sedation or general anaesthesia. Double port method facilitates full inspection of the area of interest, electrocoagulation of the site of bleeding and lysis of adhesions requiring coagulation. The point of entry for endoscope is generally near the mid-axillary line, most commonly in the fifth, sixth or seventh intercostal space within the axillary triangle. Pleural space should be freely accessible allowing easy introduction of thoracoscope with accessories into the pleural cavity and their smooth manoeuvring within the pleural cavity without causing any injury to lung or other organs. In the presence of pre-existing large pleural effusion or pneumothorax, trocar can be easily introduced without the risk of causing injury to the lung. Presence of at least 100–200 ml fluid or air should be present in the pleural cavity for the introduction of trocar/instruments without any risk of causing injury. Ultrasonographic localisation and prior needle aspiration of pleural fluid are recommended for selecting a suitable and safe site for thoracoscopic insertion.[69,70] To create adequate pleural space, 100–200 ml of air can be introduced into the pleural space through a needle after ascertaining that the tip of the needle is in the pleural cavity by aspirating pleural fluid.

2.7. Anaesthesia

Thoracoscopy can be done under local or general anaesthesia.[34,61,66,67,71–73] Generally speaking, more simple procedures, such as parietal pleural biopsies or pleurodesis with talc, can be done safely under local anaesthesia with conscious sedation. General anaesthesia, endotracheal intubation and single lung ventilation are preferred in patients requiring more complex thoracoscopic interventions, such as decortication, and in those with certain co-morbidities, such as heart failure, obesity or those unable to lie on the side for more than an hour.

Patient should be explained about the procedure to relieve anxiety. Premedication with Injection atropine to minimise vasovagal reactions and hydrocodone to suppress cough (in those with history of persistent cough) can be given.[34] After cleaning and draping the area with sterile towels, 15–30 mL of 1% lidocaine is injected into the chest wall – step-by-step infiltrating the skin, subcutaneous tissue, intercostal muscle, caudal rim of the upper rib and the cranial rim of the lower rib (to anaesthetise the intercostal nerve as well as the periosteum of the ribs) and parietal pleura. While infiltrating local anaesthetic agent, extreme caution should be exercised by repeated aspiration to avoid injection into a blood vessel, especially intercostal artery. To maximise comfort and to make procedure pain free, patient should be conscious yet well sedated without any haemodynamic and respiratory compromise. This can be achieved by the judicious administration of a narcotic analgesic, such as morphine or fentanyl, and a sedative, such as propofol or midazolam, in appropriate doses either singly or in combination. The procedure is done with proper monitoring of heart rate, blood pressure and oxygen saturation.

2.8. Technique

Insertion of thoracoscope is similar to chest tube insertion by means of a trocar.[34,67] At the point of entry, an incision, approximately 10 mm, is made using a scalpel in mid intercostal space parallel to rib. The wound can be enlarged by means of artery forceps. This is followed by careful insertion of the trocar with cannula through the incision into the pleural space by applying corkscrew motions until the sudden release of resistance is felt. The cannula is kept in situ about 1–3 cm within the pleural cavity while the trocar is removed. In case adequate freely accessible pleural space is not available, blunt dissection technique is preferred for inserting the trocar and creating pneumothorax. The thoracoscope is advanced into the pleural cavity under direct vision through the trocar and the pleural fluid is removed completely

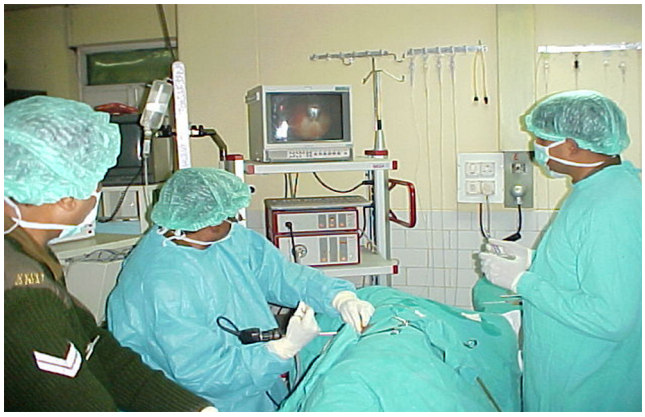


Fig. 1 – Performance of medical thoracoscopy in bronchoscopy suite.

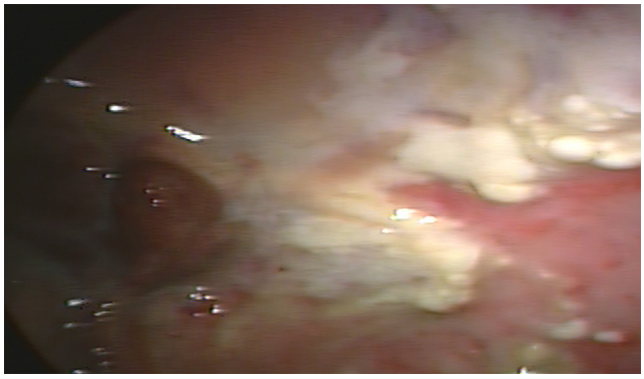


Fig. 3 – Tubercular empyema – purulent exudates over thickened and nodular pleura.

through the working channel of the semi-rigid pleuroscope or by inserting the catheter separately in the port. While the fluid is being removed, the atmospheric air spontaneously gushes into the pleural cavity through the thoracoscopic port and negates the risk of life threatening re-expansion pulmonary oedema that occurs otherwise following large volume pleural fluid aspiration through a closed system. The thoracoscope is gently manoeuvred inside the pleural cavity to carry out thorough inspection of the entire pleural cavity including the visceral pleura over lung surface and parietal pleura over mediastinum, diaphragm and chest wall. The findings observed at thoracoscopy are recorded. To facilitate easy movements of thoracoscope by the operator, adhesions between visceral and parietal pleura and pockets of loculation should be disrupted either mechanically or by electrocautery. The second port of entry if considered necessary is selected at a suitable site under endoscopic vision, usually one intercostal space superior or inferior to the primary port of entry.[60]

Selective biopsy from areas of abnormality on the pleural or lung surface should be carried out and sufficient quantity of tissue should be obtained for comprehensive study by using optical biopsy forceps introduced through the working channel (Fig. 1) or through a separate port. Normally, 10 or more biopsies

Fig. 2 – Specimen of pleural tissue obtained by thoracoscopic pleural biopsy.

are taken from areas of abnormality including those on chest wall, lung surface, diaphragm and mediastinum (Fig. 2). It is recommended to identify thickening/nodularity on the parietal pleura by palpating the lesion with the help of a closed biopsy forceps and to perform biopsy by peeling/striping the area after grasping the lesion by a biopsy forceps. To avoid inadvertent injury to neurovascular bundle, pleural biopsy should be performed over a hard surface of the rib. While taking biopsy, blood vessels and emphysematous lung surface must be avoided and hemostasis and no air leak following the procedure must be ensured. It is recommended to take fibrinous material and fluid from loculated effusions, especially from the lung bases for mycobacterial studies as they have higher yield. About 50 mL of pleural fluid should be collected and sent for biochemistry, cytology and infectious cultures. The biopsy specimen should be sent for TB bacteriology, histopathology and other tests, as deemed necessary according to clinical situation of the case. After the completion of thoracoscopic procedure, once again the pleural cavity is inspected for any air leak or bleeding point for additional intervention if felt necessary. This is followed by the insertion of a suitable sized chest tube, normally 28 F, into the pleural cavity through thoracoscopic port. The tip of the chest tube with side holes is positioned appropriately in the pleural cavity (usually apico-posteriorly) for optimum drainage of residual air/fluid from the pleural cavity. The wound of port of entry is closed and chest drain is anchored to the skin with sutures. The chest tube is connected to underwater seal and gentle step-by-step continuous negative suction (−15 to −20 cm H_2O) is applied until complete re-expansion of the lung has been achieved. In most cases, chest drain can be removed within 24 h. Longer duration of chest tube drainage is warranted if there is rapid re-accumulation of fluid or persistent air leak. Post-procedure management involves care of the chest drain and close monitoring for any cardio-respiratory and haemodynamic compromise.

2.9. *Thoracoscopic findings in tuberculous pleural effusion*

Medical thoracoscopy provides wealth of information regarding various pathological changes observed in tuberculosis.[44,74,75]

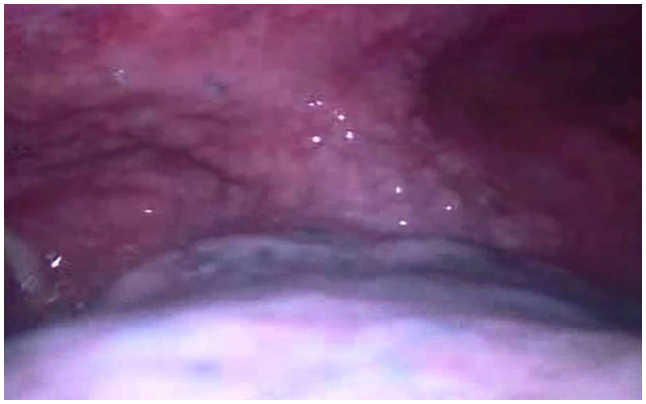


Fig. 4 – Pleural cavity showing multiple nodules covered with thin fibrin over parietal pleura adjacent to lung.

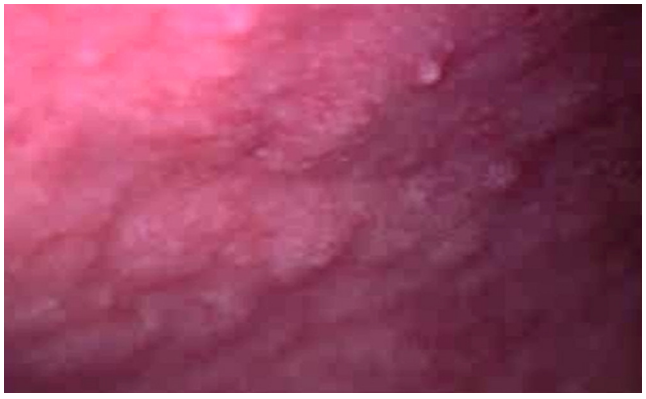


Fig. 5 – Disseminated small sago-like nodules and large nodules over parietal pleura.

Diffuse inflammatory changes in the pleura-fibrinous exudation, abundant fibrinous membranes, septae formation and areas of necrosis are common findings observed at thoracoscopy (Fig. 3). Sometimes, areas of fibrosis, pleural thickening, calcification and varying degree of seeding of the pleural surface with solid or caseous, sago-like nodules with scanty fibrin deposits can be observed. Presence of large conglomerate nodules may be seen and confused with disseminated malignant nodules (Figs. 4 and 5).

2.10. *Complications*

In experienced hands, medical thoracoscopy is a safe and an effective procedure with hardly any major complications.[34,76] Proper patient selection and close monitoring during and after the procedure is required to minimise morbidity and mortality. Minor complications by and large do not require any specific interventions. Mortality rate for medical thoracoscopy is less than 0.5%, often unrelated to procedure. The most serious and rare complication is air or gas embolism during the induction of pneumothorax by gas or by air (<0.1%) and can be prevented if appropriate precautionary measures are taken. Other complications include pain, persistent air leak, hypoxaemia, cardiac arrhythmias, hypotension (due to large volume pleural fluid aspiration), bleeding, postoperative fever, wound infection, subcutaneous emphysema and empyema and are eminently preventable. Complications due to medical thoracoscopy are much lower than of VATS. Overall mortality of 2% was reported for VATS.[77,78]

2.11. *Advantages of medical thoracoscopy*

Medical thoracoscopy offers diagnostic accuracy of almost 100% for tuberculosis as compared to 28–88% reported for closed needle biopsy and less than 20% for pleural fluid culture.[75,79–88] Low diagnostic yield by closed needle biopsy is expected in early stages of the disease as the lesions are difficult to access (by closed pleural biopsy) being few in number and often scattered over pleura covering diaphragm, mediastinum and lower costal surface of chest wall. The tissue obtained by closed pleural biopsy often is inadequate. Unfortunately, the diagnostic yield of closed pleural biopsy for malignancy as well as other pathologies is much lower, less than 45%.[29] Trans-thoracic needle pleural biopsies from suspicious nodule under CT guidance using either a Tru-cut biopsy or Abrams needle have a diagnostic sensitivity of 87% compared to 47% by closed pleural biopsy in malignancy.[87] In tuberculosis, definite nodule may not be evident on imaging and subtle pleural changes may not be picked up by imaging for selective CT-guided biopsy. Due to the relatively high number of undiagnosed exudative effusions even after extensive pleural fluid analysis and closed pleural biopsy, medical thoracoscopy is warranted to establish the diagnosis.

Thoracoscopy facilitates fast and accurate diagnosis of exudative pleural effusions of undetermined aetiology with a high diagnostic yield.[29,89] In low prevalence areas for TB, medical thoracoscopy not only confirms TB but also accurately excludes other causes of exudative pleural effusions especially malignancy. Large retrospective cohort studies of several thousand patients have shown that for malignancy, the sensitivity is in the range of 93–95%, whereas for tuberculosis, it approaches 100%.[29] In malignant pleural effusions, false negative diagnostic reports for medical thoracoscopy is less than 10%. Medical thoracoscopy permits proper visualisation of major portions of pleura and adequate tissue sampling under direct vision from abnormal/suspicious areas inside the pleural cavity including those that are inaccessible or difficult to access without injuring vital structures, such as diaphragm, liver or spleen, by closed pleural methods. Mycobacterial study on tissue samples obtained at thoracoscopy, such as membranes

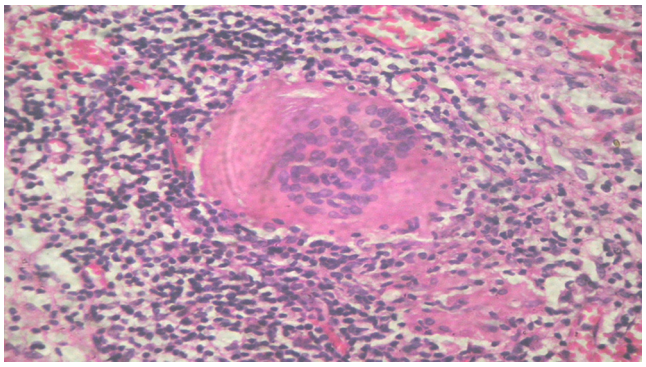


Fig. 6 – Histopathology depicting tubercular granuloma.

and fibrinous material, has a diagnostic sensitivity of 87%, exceeding that obtained by the closed biopsy.[79] Presence of caseating granulomas, a hallmark feature of tuberculosis, may not be present and histopathology of pleura often reveals noncaseating granulomas (Fig. 6). In a clinical setting of tuberculosis, demonstration of granulomatous pleuritis is sufficient to make a diagnosis as 95% granulomatous pleuritis is due to tuberculosis. Appropriate therapy with anti-tubercular therapy pending culture report can be started in those with findings highly suggestive of tuberculosis and drug therapy is modified if drug resistance is confirmed by culture. In cases where diagnosis remains indeterminate even after extensive evaluation including medical thoracoscopy, a careful follow-up of such cases by the conservative approach of watchful waiting is quite appropriate.[29,34] In future, the diagnostic accuracy of medical thoracoscopy is likely to be enhanced further by the use of auto-fluorescence video-thoracoscopy or narrowband imaging during medical thoracoscopy.[55,57,90,91] In addition, in indeterminate cases, repeated medical thoracoscopy is feasible.[92]

Thoracoscopy allows disruption of pleural adhesions and peeling/debridement of large membranes. It permits complete evacuation of fluid and air and facilitates early and complete expansion of the underlying lung. It enables selection of an appropriate chest drain of sufficient size and length and its exact placement inside the pleural cavity for maximising drainage and minimising patient discomfort. These measures are expected to improve the clinical course in terms of more rapid resolution of effusion, shorter hospital stays, improved lung function and minimised disability due to fibrothorax.[75]

3. Conclusions

Father of medical thoracoscopy – Hans-Christian Jacobaeus, had a clear vision regarding the role of pleuroscopy in the management of tuberculosis and he realised his vision by ably utilising his newly discovered technique with excellent outcome when the technology and medical facilities were suboptimal. Now after more than a century since Jacobaeus operation, the role of medical thoracoscopy has been well defined and there is a large body of evidence to validate the safety, diagnostic accuracy and maximum therapeutic utility of this less invasive procedure so as to justify its eminent place in the practice of thoracic medicine. Currently, Pulmonologists are at a great advantage, thanks to availability of safe anaesthesia, sophisticated user-friendly equipments and standard guidelines to safely practice this procedure and optimise its utility. Thoracoscopy should no longer be neglected by Pulmonologists[93] and should be used optimally in areas where tuberculous pleural effusion is endemic and its management a major concern. Undoubtedly there is resurgent interest among pulmonologists to practice medical thoracoscopy, now considered a "gold standard" for the study of tuberculous pleural effusion.

Conflicts of interest

The author has none to declare.

REFERENCES

1. Global tuberculosis control. A short update to the 2009 report. World Health Organisation. WHO/HTM/TB/2009, 426.
2. TB India 2014. *RNTCP Status Report, Central TB Division*. Ministry of Health & Family Welfare; March 2014.
3. al-Qorain A, Larbi EB, al-Muhanna F, et al. Pattern of pleural effusion in Eastern provision of Saudi Arabia: a prospective study. *East Afr Med J*. 1994;71:246–249.
4. Valdes L, Alvarez D, Valle JM, et al. The etiology of pleural effusions in area with high incidence of tuberculosis. *Chest*. 1996;109:158–162.
5. Ferrer J. Pleural tuberculosis. *Eur Resp J*. 1997;10:942–947.
6. Aggarwal N, Gupta D, Jindal SK. Diagnosis of tuberculous pleural effusion. *Indian J Chest Dis Allied Sci*. 1999;41(2):89–100.
7. Sharma SK, Mohan A. Extra pulmonary tuberculosis – review article. *Indian J Med Res*. 2004;120:316–353.
8. Light RW. *Pleural Diseases*. 5th edition Baltimore, MD: Lippincott Williams & Wilkins; 2007.
9. Gopi A, Madhavan SM, Sharma SK, Sahn SA. Diagnosis and treatment of tuberculous pleural effusion in 2006. *Chest*. 2007;131(3):880–889.
10. Saks AM, Posner R. Tuberculosis in HIV positive patients in South Africa: a comparative radiological study with HIV negative patients. *Clin Radiol*. 1992;46:387–390.
11. Awil PO, Bowlin SJ, Daniel TM. Radiology of pulmonary tuberculosis and human immunodeficiency infection in Gulu, Uganda. *Eur Respir J*. 1997;10:615–618.
12. Pozniak AL, MacLeod GA, Ndlovu D, et al. Clinical and chest radiographic features of tuberculosis associated with human immunodeficiency virus in Zimbabwe. *Am J Respir Crit Care Med*. 1995;152:1558–1561.
13. Basu A, Chakrabarty I, Ghosh N, Chakraborty S. A clinicopathological study of tuberculous pleural effusion in a tertiary care hospital. *Ann Trop Med Public Health*. 2012;5:168–172.
14. Ibrahim WH, Ghadban W, Khinji A, et al. Does pleural tuberculosis disease pattern differ among developed and developing countries. *Resp Med*. 2005;99:1038–1045.
15. Moudgil H, Sridhar G, Leitch AG. Reactivation disease: the commonest form of tuberculous pleural effusion in Edinburg, 1980-1991. *Resp Med*. 1994;88:301–304.
16. Berger HW, Mejia E. Tuberculous pleurisy. *Chest*. 1973;63:88–92.
17. Richter C, Perenboom R, Mtoni I, et al. Clinical features of HIV-seropositive and seronegative patients with tuberculous pleural effusion in Dar es Salaam, Tanzania. *Chest*. 1994;106:1471–1475.
18. Heyderman RS, Makunike R, Muza T, et al. Pleural tuberculosis in Harare, Zimbabwe: the relationship between human immunodeficiency virus, CD4 lymphocyte count, granuloma formation and disseminated disease. *Trop Med Int Health*. 1998;3:14–20.
19. Valdes L, Alvarez D, San Jose E, et al. Tuberculous pleurisy: a study of 254 patients. *Arch Intern Med*. 1998;158:2017–2021.
20. Maher GG, Berger HW. Massive pleural effusion: malignant and non-malignant causes in 46 patients. *Am Rev Respir Dis*. 1972;105:458–460.
21. Chan CH, Arnold M, Chan CY, et al. Clinical and pathological features of tuberculous pleural effusion and its long-term consequences. *Respiration*. 1991;58:171–175.
22. Light RW. Update on tuberculous pleural F effusion. *Respirology*. 2010;15:451–458.
23. Ocana I, Martinez-vazquez JM, Segura RM, et al. Adenosine deaminase in pleural fluids: test for diagnosis of tuberculous pleural effusion. *Chest*. 1983;84:51–53.

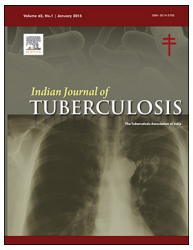
24. Villena V, Lopez-Encuentra A, Pozo F, et al. Interferon gamma levels in pleural fluid for the diagnosis of tuberculosis. *Am J Med*. 2003;115:365–370.
25. Lee YCG. Pleural anatomy and fluid analysis. In: Ernst A, Herth FJF, eds. In: *Principles and Practice of Interventional Pulmonology*. New York: Springer Science + Business Media; 2013:545–555.
26. Levine H, Szanto PB, Cugell DW. Tuberculous pleurisy: an acute illness. *Arch Intern Med*. 1968;122:329–332.
27. Jones D, Lieb T, Narita M, et al. Mesothelial cells in tuberculous pleural effusions of HIV-infected patients. *Chest*. 2000;117:289–291.
28. Frank W. Tuberculous pleural effusion. In: Loddenkemper R, Anthony VB, eds. In: *Pleural Diseases, European respiratory monograph, 22*. Sheffield: European Respiratory Society Journals; 2002:219–233.
29. Michaud G. Approach to unclear exudates. In: Ernst A, Herth FJF, eds. In: *Principles and Practice of Interventional Pulmonology*. New York: Springer Science + Business Media; 2013:675–680.
30. Ruiz-Manzano J, Monterola JM, Gamboa F, et al. Detection of mycobacterium tuberculosis in paraffin embedded pleural biopsy specimens by commercial ribosomal RNA and DNA amplification kits. *Chest*. 2000;118:648–655.
31. Conde MB, Loivos AC, Rezende VM, et al. Yield of sputum induction in the diagnosis of pleural tuberculosis. *Am J Respir Crit Care Med*. 2003;167:723–725.
32. Light RW. Pleural effusions. *Med Clin N Am*. 2011;95:1055–1070.
33. Luzze H, Elliot AM, Joloba ML, et al. Evaluation of suspected tuberculous pleural pleurisy: clinical and diagnostic findings in HIV-positive and HIV-negative adults in Uganda. *Int J Tuberc Lung Dis*. 2001;5:746–753.
34. Loddenkemper R. Thoracoscopy/pleuroscopy. In: Ernst A, Herth FJF, eds. In: *Principles and Practice of Interventional Pulmonology*. New York: Springer Science + Business Media; 2013:605–621.
35. Cruise F. The utility of endoscope as an aid in the diagnosis and treatment of disease. *Dublin Q J Med Sci*. 1865;39:329–363.
36. Jacobaeus HC. Üeber die Möglichkeit, die Zystoskopie bei Untersuchung seröser Höhlungen anzuwenden. *Munch Med Wochenschr*. 1910;40:2090–2092.
37. Jacobaeus HC. The practical importance of thoracoscopy in surgery of the chest. *Surg Gynecol Obstet*. 1922;34:289–296.
38. DeFrancis N, Klosk E, Albano E. Needle biopsy of the parietal pleura. A preliminary report. *N Engl J Med*. 1955;252:948–949.
39. Bergquist S, Nordenstam H. Thoracoscopy and pleural biopsy in the diagnosis of pleurisy. *Scand J Respir Dis*. 1966;47:64–74.
40. Sattler A. Die Bedeutung der endoskopischen Untersuchung des Pleuraraums fur die Diagnostik und Therapie. *Méd Hyg*. 1968;26:630–638.
41. Brandt HJ, Mai J. Differential diagnose des Pleuraergusses durch Thorakoskopie. *Pneumologie*. 1971;145:192–203.
42. Boutin C, Viallat JR, Cargnino P, et al. La Thoracoscopie en 1980. Revue générale. *Poumon Coeur*. 1981;37:11–19.
43. Brandt HJ, Loddenkemper R, Mai J. *Atlas of Diagnostic Thoracoscopy. Indications – Technique*. New York: Thieme; 1985.
44. Boutin C, Viallat JR, Aelony Y. Diagnostic thoracoscopy for pleural effusions. In: Boutin C, Viallat JR, Aelony Y, eds. In: *Practical Thoracoscopy*. Berlin: Springer; 1991:51–64.
45. Marchetti GP, Tassi G. Thoracoscopy. An old technique for a modern work-up of the pleural cavity. In: Astoul P, ed. et al. In: *Thoracoscopy for Pulmonologists*. Berlin/Heidelberg: Springer-Verlag; 2014:5–17.
46. Gossot D, Kleinmann P, Levi JE. *Surgical Thoracoscopy*. Paris: Springer; 1994.
47. Krasna MJ, Mack MJ. *Atlas of Thoracoscopic Surgery*. St Louis: Quality Medical Publishing; 1994.
48. Inderbitzi R. *Surgical Thoracoscopy*. Berlin: Springer; 1995.
49. Mathur PN, Astoul P, Boutin C. Medical thoracoscopy. Technical details. *Clin Chest Med*. 1995;16:479–486.
50. Loddenkemper R. Thoracoscopy – state of the art. *Eur Respir J*. 1998;11:213–221.
51. Antony VB, Loddenkemper R, Astoul P, et al. Management of malignant pleural effusions. ATS/ERS Statement. *Am J Respir Crit Care Med*. 2000;162:1987–2001. Eur Respir J. 2001;18:402–419.
52. Lee P, Mathur PN, Colt HG. Advances in thoracoscopy: 100 years since Jacobaeus. *Respiration*. 2010;79:177–186.
53. Colt HG, Lee P. Rigid and semirigid pleuroscopy: the future is bright. *Respirology*. 2005;10:418–425.
54. Munnavar M, Kan MA, Edwards J, Waqarrudin Z, Mills J. The autoclavable semirigid thoracoscope: the way forward in pleural disease? *Eur Respir J*. 2007;29:571–574.
55. Schönfeld N, Schwarz J, Kollmeier J, et al. Narrow band imaging (NBI) during medical thoracoscopy: first impressions. *J Occup Med Toxicol*. 2009;4:24–28.
56. Tassi G, Marchetti GP. Minithoracoscopy. In: Astoul P, ed. et al. In: *Thoracoscopy for Pulmonologists*. Berlin/Heidelberg: Springer-Verlag; 2014:227–235.
57. Chrysanthidis MG. Autofluorescence and thoracoscopy. In: Astoul P, ed. et al. In: *Thoracoscopy for Pulmonologists*. Berlin/Heidelberg: Springer-Verlag; 2014:237–252.
58. Ernst A, Silvestri GA, Johnstone D. Interventional pulmonary procedures. Guidelines from the American College of Chest Physicians. *Chest*. 2003;123:1693–1717.
59. Lamb CR, Feller-Kopman D, Ernst A, et al. An approach to interventional pulmonary fellowship training. *Chest*. 2010;137:195–199.
60. Hooper CE, Lee YCG, Maskell NA. Setting up a specialist pleural disease service. *Respirology*. 2010;15:1028–1036.
61. Horswell JL. Anesthetic techniques for thoracoscopy. *Ann Thorac Surg*. 1993;56:624–629.
62. Buchanan DR, Neville E. *Thoracoscopy for Physicians: A Practical Guide*. London: Arnold Publishers; 2004:166.
63. Rodriguez-Panadero F, Janssen JP, Astoul P. Thoracoscopy: general overview and place in the diagnosis and management of pleural effusion. *Eur Respir J*. 2006;28:409–421.
64. Lee P, Colt HG. State of the art: pleuroscopy. *J Thorac Oncol*. 2007;2:663–670.
65. Lee P, Colt HG. A spray catheter technique for pleural anesthesia: a novel method for pain control before talc poudrage. *Anesth Analg*. 2007;104:198–200.
66. Delage A, Marquette CH. Anaesthesiology for thoracoscopy. In: Astoul P, ed. et al. In: *Thoracoscopy for Pulmonologists*. Berlin/Heidelberg: Springer-Verlag; 2014:53–58.
67. Astoul P, Tassi G, Tschopp JM. Introduction to the pleura and thoracoscopic technique. In: Astoul P, ed. et al. In: *Thoracoscopy for Pulmonologists*. Berlin/Heidelberg: Springer-Verlag; 2014:59–82.
68. Lee P, Hsu A, Lo C, et al. Prospective evaluation of flex-rigid pleuroscopy for indeterminate pleural effusion: accuracy, safety and outcome. *Respirology*. 2007;12:881–886.
69. Hersh C, Feller-Kopman D, Wahidi M, et al. Ultrasound guidance for medical thoracoscopy: a novel approach. *Respiration*. 2003;70:299–301.
70. Diacon A, Brutsche M, Soler M. Accuracy of pleural puncture sites: comparison of clinical examination with ultrasound. *Chest*. 2003;123:436–441.
71. Migliore M, Giuliano R, Aziz T, Saad RA, Sgalambro F. Four-step local anesthesia and sedation for thoracoscopic diagnosis and management of pleural diseases. *Chest*. 2002;121:2032–2035.
72. Rahman NM, Ali NJ, Brown G, et al. Local anaesthetic thoracoscopy: British Thoracic Society pleural disease guideline 2010. *Thorax*. 2010;65(suppl 2). ii54–60.

73. Tschopp JM, Purek L, Frey JG, et al. Titrated sedation with propofol for medical thoracoscopy: a feasibility and safety study. *Respiration*. 2011;82:451–457.
74. Loddenkemper R, Mathur PN, Noppen M, Lee P. *Medical Thoracoscopy/pleuroscopy: Manual and Atlas*. Stuttgart/New York: Thieme; 2011.
75. Frank W, Schonfeld N. Diagnostic thoracoscopy: non malignant pleural effusion. In: Astoul P, ed. et al. In: *Thoracoscopy for Pulmonologists*. Berlin/Heidelberg: Springer-Verlag; 2014:121–139.
76. Rodríguez-Panadero F, Romero BR. Complications of thoracoscopy. In: Astoul P, ed. et al. In: *Thoracoscopy for Pulmonologists*. Berlin/Heidelberg: Springer-Verlag; 2014209–217.
77. Hazelrigg SR, Nunchuck SK, LoCicero J, The Video Assisted Thoracic Surgery Study Group. Video assisted thoracic surgery study group data. *Ann Thorac Surg*. 1993;56:1039–1044.
78. Jacovici R, Lang-Lazdunski L, Pons F, et al. Complications of video-assisted thoracic surgery: a five-year experience. *Ann Thorac Surg*. 1996;61:533–537.
79. Loddenkemper R. Thoracoscopy: results in noncancerous and idiopathic pleural effusions. *Poumon Coeur*. 1981;37:261–264.
80. Loddenkemper R, Boutin C. Thoracoscopy: present diagnostic and therapeutic indications. *Eur Respir J*. 1993;6:1544–1555.
81. Colt HG. Thoracoscopy: window to the pleural space. *Chest*. 1999;116:1409–1415.
82. Seijo LM, Sterman DH. Interventional pulmonology. *N Engl J Med*. 2001;344:740–749.
83. Loddenkemper R. Medical thoracoscopy. In: Light RW, Lee YCG, eds. In: *Textbook of Pleural Diseases*. London: Arnold Publishers; 2003:498–512.
84. De Groot M, Walther G. Thoracoscopy in undiagnosed pleural effusions. *S Afr Med J*. 1998;88:706–711.
85. Emad A, Rezaian GR. Diagnostic value of closed percutaneous pleural biopsy vs pleuroscopy in suspected malignant pleural effusion or tuberculous pleurisy in a region with a high incidence of tuberculosis: a comparative age dependent study. *Respir Med*. 1998;92:488–492.
86. Diacon AH, Van deWal BW, Wyser C, et al. Diagnostic tool in tuberculous pleurisy: a direct comparative study. *Eur Respir J*. 2003;22:589–591.
87. Maskell NA, Gleeson FV, Davies RJ. Standard pleural biopsy versus CT-guided cutting needle biopsy for diagnosis of malignant disease in pleural effusions: a randomised controlled trial. *Lancet*. 2003;361:1326–1330.
88. Maldhure BR, Bedarkar SP, Kulkarni HR, Papinwar SP. Pleural biopsy and adenosine deaminase in pleural fluid for the diagnosis of tubercular pleural effusion. *Indian J Tuberc*. 1994;41:161–165.
89. Mootha VK, Agarwal R, Singh N, Aggarwal AN, Gupta D, Jindal SK. Medical thoracoscopy for undiagnosed pleural effusions: experience from a tertiary care hospital in north India. *Indian J Chest Dis Allied Sci*. 2011;53:21–24.
90. Chrysanthidis MG, Janssen PJ. Auto fluorescence video thoracoscopy in exudative pleural effusions: preliminary results. *Eur Respir J*. 2005;26:989–992.
91. Froudarakis ME. Advanced medical thoracoscopy-pleuroscopy procedures. In: Ernst A, Herth FJF, eds. In: *Principles and Practice of Interventional Pulmonology*. New York: Springer Science + Business Media; 2013:631–637.
92. Breen D, Fraticelli A, Greillier L, Mallawathantri S, Astoul P. Redo medical thoracoscopy is feasible in patients with pleural diseases – a series. *Interact Cardiovasc Thorac Surg*. 2009;8:330–333.
93. Astoul P, Tassi GF, Tschopp JM. The safety profile of medical thoracoscopy: expert advices and recommendations. In: Astoul P, ed. et al. In: *Thoracoscopy for Pulmonologists*. Berlin/Heidelberg: Springer-Verlag; 2014:207.

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: http://www.journals.elsevier.com/indian-journal-of-tuberculosis/



Continuing Medical Education

Drug resistance among TB cases and its clinical implications

K.K. Chopra *

New Delhi Tuberculosis Centre, New Delhi, Delhi 110002, India

ARTICLE INFO

Article history:
Received 18 March 2015
Accepted 10 August 2015
Available online 9 October 2015

Keywords:
Drug resistance
TB
Clinical implication

ABSTRACT

The emergence of *M. tuberculosis* strains resistant to at least, Isoniazid (INH) and Rifampicin (RIF), the two most potent drugs of first-line anti-TB therapy is termed multidrug drug-resistant TB (MDR-TB). This is a cause of concern to TB Control Programmes worldwide. When MDR-TB strains become resistant to the major second-line drugs, one of the fluoroquinolones and one of the three injectable drugs (Amikacin, Kanamycin and Capreomycin), it is defined as extensively drug resistant TB.[1,2]

MDR-TB is a manmade, costly and deadly problem. Rapid diagnosis of MDR-TB is essential for the prompt initiation of effective second-line therapy to improve treatment outcome and limit transmission of the disease.

1. Global burden

Cases of multidrug drug-resistant TB (MDR-TB) have been reported in every country.[1,2] As of 2014, 3.5% of new TB cases have MDR-TB.[3] Levels are much higher in those previously treated for TB (about 20%). Approximately 0.5 million new MDR-TB cases were estimated in the world in 2011.[4] About 60% of these cases occurred in Brazil, China, India, the Russian Federation and South Africa. Estimated number of MDR-TB cases in 2011 were reported to be 630,000 out of an approximate of 12 million prevalent TB cases. In 2014, MDR-TB estimated cases were reported to be 424,203, which included both new and previously treated cases, whereas in 2000, the estimate was 272,906.[1,5]

2. Indian scenario

India has the highest estimated MDR-TB cases amongst notified TB patients in the world with estimated MDR-TB emerging annually to 99,000.[3] Data from studies conducted by NIRT and NTI have found MDR-TB levels of 1–3% in new cases and around 12% in re-treatment cases. RNTCP has recently undertaken three community-based state level drug resistance surveillance (DRS) studies in Gujarat, Maharashtra and Andhra Pradesh. These surveys have estimated the prevalence of MDR-TB to be about 3% in new cases and 12–17% in re-treatment cases. XDR among MDR-TB isolates in Gujarat and Andhra Pradesh survey were 3–7%, while ofloxacin resistance in these two states surveys was 21–24%.

* Tel.: +91 01123239056.
E-mail address: chopra_drkk@yahoo.co.in

http://dx.doi.org/10.1016/j.ijtb.2015.08.001

3. Causes of increase in drug-resistant tuberculosis

Suboptimal TB control practices (e.g., poor DOT, inadequate infection control measures, and treatment without drug susceptibilities or culture) are the major cause in MDR-TB. From a microbiological perspective, the resistance is caused by genetic mutation that makes a drug ineffective against the mutant bacilli. An inadequate or poorly administered treatment regimen allows drug-resistant mutants to become the dominant strain in a patient infected with TB.

4. Programmatic management of drug resistant TB (PMDT) Services in India

After successfully establishing the DOTS services across the country in 2006, RNTCP rolled out the PMDT services in 2007.[6] There was an exponential scale up during 2011–12 to achieve complete population coverage in March 2013. PMDT prioritises diagnosis and management of M/extensively drug resistant TB (XDR-TB) cases and mono- and Poly-FLD resistant cases without M/XDR-TB treated with FLD regimes. Early implementing states used phenotypic DST for the diagnosis of DR-TB. Since 2012, all patients undergo rapid molecular DST (mostly LPA) for diagnosis. Criteria for MDR-TB are as follows:

- Criteria A
  - All new TB patients failing first-line regimen
  - All previously treated patients who remain smear-positive at the end of extended IP or later (CAT II)
  - Smear-positive contacts of known MDR cases
- Criteria B
  - All Sm +ve re-treatment PTB cases at diagnosis
  - Any Sm +ve follow-up of new or RT cases
- Criteria C
  - Sm −ve re-treatment PTB cases at diagnosis
  - HIV TB co-infected cases

5. TB diagnostics

The care of patients with tuberculosis (TB) starts with a quality assured diagnosis. Arguably, the most important component of health systems is the laboratory services. An unprecedented effort to improve and expand TB laboratory capacity is under way, spearheaded by WHO and the Stop TB Partnership, Global Laboratory Initiative and its network of international collaborators. For an increased output, a given lab can conduct DST on many more patients by molecular and liquid than solid culture method. The rapid diagnosis reduces patient loss, mortality and operational complexity of current system. The infrastructure requires flexible capacity, with molecular, solid and liquid capacity for testing. Thus, for DST at certified laboratory, wherever available Molecular DST (e.g. Line Probe Assay (LPA)) is preferred diagnostic method because of the rapid and highly accurate rifampicin results, followed in preference by Liquid C-DST and then Solid C-DST. Similarly for follow-up cultures, wherever available, liquid culture will be preferred over solid culture. However, this will be liquid cultures for at least the crucial months of follow-up (IP-3, 4, 5, 6 and CP-18, 21, 24) and over and beyond this, it will be determined by the workload of individual laboratories.

6. Non-MDR-TB cases in India

Currently, there is no policy for the management of non-MDR cases in India. New smear positive cases remaining positive after 2 or 3 months of therapy are continued on the same regimen. Also smear positive retreatment cases at baseline are initiated on retreatment regimen, i.e., Cat II. If they remain positive after 3 or 4 months of treatment, same schedule is continued, and DST is repeated for patients failing to first-line category treatment.

To know the prevalence of non-MDR-TB cases, data of about 7000 cases treated under programmatic conditions were reviewed to find out prevalence of resistance to individual drug and treatment outcome of such patients taking either Cat I or Cat II treatment. Data revealed H mono resistance to the tune of 34% (17% among Cat I and 83% among Cat II patients). Among these cases, failure rate was around 49%. Worse than this on repeat DST, there was implication of resistance up to 40% against rifampicin among these patients.

Clinical implications include treating mono- and poly-resistant cases, in which first-line regimen is associated with high risk of unfavourable outcomes including failure to treatment. This risk increases with the number of drugs, against which the bacilli are resistant. Significant risk of amplification of resistance to rifampicin was observed in mono- and poly-resistant patients treated with FLD.

On the other hand, in a study conducted in NDTB Centre (unpublished data) among 1200 MDR suspects, 12% were found to be pan sensitive on DST. Patients got Cat I or Cat II treatment, based on previous history of anti-TB treatment. Their treatment outcome was correlated. Only 60% cases responded to treatment. More than 14% cases failed to treatment may be due to in vitro, in vivo variation in susceptibility of organisms. Some of them may have taken irregular treatment.

Baseline second-line DST among confirmed MDR cases also found 22% strains resistant to ofloxacin and 2% to both ofloxacin and kanamycin. Impact on treatment outcome and implication of resistance to other drugs is yet to be seen.

7. Effect of drug resistance on treatment outcome with first-line drugs (FLDs)

The effect of drug resistance on the outcome of TB treatment using standard regimens depends on type and number of drugs to which the strain is resistant versus the potency of treatment regimen.

Modern first-line short-course treatment regimens for TB use R for the full 6-month duration. R resistance leads to

increased rates of failure or relapse, depending on sensitivity to other drugs in the regimen (H, Z, E, sometimes S). Using only FLDs, MDR-TB has less than 50% chance of relapse-free cure, barely better than natural course of untreated TB. H monoresistance has little impact on the treatment outcome. Influence of E monoresistance is not known because it is very rare and less reliable DST. Influence of Z monoresistance is also unclear, however initial Z resistance would be expected to lead to increased relapse. Resistance to H with E or S increases risk of failure and relapse to approximately 10% patients using R-throughout regimen, 40% without R regimen in CP. Resistance to H + E + S leads to failure to any FL regimen in approximately 1/3 to 1/2 of patients, due to acquisition of R resistance with the strain developing into true MDR-TB. Because of poor growth of some MDR-TB strains, concomitant R resistance may be missed by conventional DST. It is the probable cause of more failures among retreatment patients with initial H-resistant, R-susceptible disease.[7]

8. Amplification of drug resistance

Except for MDR-TB and combined resistance to H, S and E, majority of patients with initial drug resistance will be cured using standard FLD regimen. Risk of amplification of resistance with development of MDR-TB in failure cases is a real problem. Because of poor growth of some MDR-TB strains, concomitant R resistance may be missed by conventional DST. This can be a possible explanation for studies reporting significantly more failures among retreatment cases with initially H-resistant, R-susceptible disease compared with the same initial resistance, but treated with less powerful 6 month R throughout regimens. It is therefore reasonable to assume that some patients who carry H or R resistant strains, but not both, will fail or relapse with an unmodified FLD regimen. The revised FLD regimen should be used with repeat rapid R DST in case of delayed conversion or even a switch to the MDR regimen at any time in first-line retreatment, with correlating clinical conditions. The alternative recommendation in some guidelines is replacing H by FQ, but this would create pre-XDR strains out of MDR strains that are difficult to grow and may be misclassified as H + E, H + S, or H + E + S-resistant.[7]

9. Effect of drug resistance on treatment outcome with SLDs

Very little data are available regarding impact of initial second-line resistance on standard MDR-TB treatment regimens. FQ resistance seems to be most important and only about 10% of those with initial FQ resistance have failed or relapsed from the regimen for 'new' MDR-TB patients. Thiomide resistance has a minimal impact on the outcome of the regimen. Resistance to thiomides in strains from patients never exposed to these drugs will often be caused by cross resistance with H, due to *inhA* mutation. The remaining SLDs (PAS and CS) have little activity and are vulnerable as these are companion drugs only. Resistance to these drugs will only matter when there is already some resistance to FQ or other companion drugs, and possibly with weaker regimens.[7]

10. Effect of drug resistance on treatment monitoring parameters

There is confusion regarding the meaning of positive smears at the end of intensive phase. Sputum smear conversion depends mainly on the extent of the disease and bacillary load at the start of the treatment, and much less on regularity of drug intake and drug resistance. Only MDR-TB clearly delays smear conversion during standard first-line treatment, even with the most powerful IP Cat II treatment – prolonged excretion of dead bacilli. In principle, culture is a better parameter for treatment monitoring. However, with referred sputum samples, results of these often paucibacillary specimens become less reliable and delays, and would reduce their usefulness. With solid media and drug-susceptible extensive disease, culture conversion often precedes smear conversion. With serious drug resistance, culture may never convert, contrary to the smear, or may revert to positive sooner than a smear.[7]

11. Are drug-resistant strains as transmissible as drug-susceptible strains?

A case–control study by Snider et al. demonstrated that contacts of patients with drug-resistant and drug-susceptible cases of TB had an equal prevalence of positive tuberculin skin test. In contrast, animal studies have shown that isoniazid-resistant strains caused significantly less disease in guinea pigs than drug-susceptible strains.[8]

12. Are drug-resistant strains likely to progress to active disease once infection is established?

In San Francisco, Burgos et al. found that strains that were resistant to isoniazid either alone or in combination with other drugs were less likely to result in secondary cases than were drug-susceptible strains. In this setting, isoniazid-resistant and MDR-TB cases were not likely to produce new, incident drug-resistant TB cases. This presumed effect on pathogenicity may be related to mutations in the *katG* gene.[9] In addition to this data, other molecular epidemiological studies observed that cases of TB caused by drug-resistant strains were less likely to be in clusters. The implication is that drug-resistant strains were less likely to be transmitted and/or to cause active TB.[10]

Factors affecting drug-resistant strains to progress to active disease are

(a) Pathogen related
- Undefined virulence factors
- Variability in virulence between genotypes
- Size of the infecting inoculum

(b) Host related
- Presence of immunosuppression
- Ethnic susceptibility to various strains

In clinical practice, often ST pattern and clinical response do not correlate. The reasons for discordant DST results are:

- Bacterial population (isolate vs. subculture)
- Differential growth kinetics
- Different inoculation methods (size, clumps)
- Different methods or media
- Cross-contamination
- Transcription and labelling errors
- MIC-critical concentration.

13. Management of MDR cases

Management decisions of a resistant case depend on finding the probable cause if prior poor adherence is recognized, may be addressed and DOT ordered. If risk of drug resistance is due to non-adherence and treatment failure is identified, drug susceptibility tests should be ordered and regimen should be changed as per history of drug intake.[11] The clinical response should be correlated with report of MDR and treatment should be changed after report of drug resistance despite a good initial response. Common errors in Management of MDR-TB cases:

(a) When initiating or revising therapy, always attempt to employ at least 3 previously unused drugs to which there is in vitro susceptibility. Common errors committed are:
  – Used 3 drugs that were part of previous failed treatment are prescribed and
  – Ethambutol and PZA are used alone for continuation phase
(b) The use of drugs to which there is demonstrated in vitro resistance is not encouraged, because there is a little or no efficacy of these drugs, e.g., ciprofloxacin resistance should have alerted providers to ofloxacin resistance because of cross resistance.
(c) Bactericidal drugs with proven efficacy should be used. Many a times Clofazamine (a weak drug with unknown efficacy) is added in regimen.
(d) 12 months of injectable therapy following culture conversion is generally recommended and exact duration determined by extent of disease and drug resistance. Many a times, streptomycin stopped after month 6.
(e) Two years of total treatment after conversion of cultures to negative is usually recommended. Occasionally patients with limited disease are declared cured after 18 months or sometimes treatment stopped at 13 months.

14. Should we treat or follow contacts to MDR/XDR?

The answer is...yes. Guidelines for MDR and drug resistance recommend following the contact for at least two years. But Data to support strategies for managing contacts are very sparse.[12]

15. Clinical Implications of resistance among TB cases

DST results must be available as soon as possible to guide treatment choices. Testing algorithms including molecular tests for rif-R may expedite decisions. Lab tests do not replace clinical judgement. Clinicians need data to interpret results based on performance parameters of the test and potential impact of prevalence of resistance on predictive value, etc. Relying on Clinical and X-ray manifestations has many limitations for the diagnosis of DR-TB as no symptoms or radiological findings differentiating susceptible from resistant TB. Prognosis and response cannot be decisively assessed through radiological examination, because lesion regression may require 3–9 month. For follow-up patients, no specific symptoms or radiological findings suggesting failure due to drug resistance, only lack of improvement compared with clinical and X-ray manifestations. Lack of improvement must be seen merely as arousing suspicion of DR-TB and supporting a request for DST. Diagnosis of DR-TB based only on clinical and radiological criteria should never be accepted, even if there is no improvement after several months of treatment.

16. Challenges for TB control programmes

Insufficient public sector MDR and XDR-TB diagnosis and treatment services is one of the main challenge as the country scaled up basic TB services via RNTCP DOTS through 2006, MDR-TB services began pilot testing only in 2007. There is poor quality of TB and MDR-TB laboratory diagnosis in the private sector. TB is often diagnosed with serology, which frequently misdiagnoses TB. The use of TB serological testing has been recommended against by RNTCP, WHO, and some expert groups from India, but such tests are widely available and widely used in the private sector. There is also lack of information about patients diagnosed with TB and MDR-TB in the private sector. Patients properly diagnosed with TB and MDR-TB in private laboratories are not notified to public health authorities.

There is irrational use and sale of anti-TB drugs and diagnostics outside the Programme. First-line TB drugs were sold to the extent of 65–117% of the estimated annual incident cases in India in private markets. Among second-line drugs, fluroquinolones are widely available with significant volume used for TB in India.

REFERENCES

1. Orenstein EW, Basu S, Shah NS, et al. Treatment outcomes among patients with multidrug-resistant tuberculosis: systematic review and meta-analysis. *Lancet Infect Dis*. 2009;9:153–161.
2. Johnston JC, Shahidi NC, Sadatsafavi M, Fitzgerald JM. Treatment outcomes of multidrug-resistant tuberculosis:

a systematic review and metaanalysis. *PLoS ONE*. 2009;4: e6914.
3. WHO. *Global Tuberculosis Report*. Geneva, Switzerland: World Health Organization; 2014.
4. WHO. *Global Tuberculosis Report*. Geneva, Switzerland: World Health Organization; 2012.
5. Zignol M, Hosseini MS, Wright A, et al. Global incidence of multidrug-resistant tuberculosis. *JID*. 2006;194.
6. *RNTCP Guidelines on Programmatic Management of Drug Resistant TB (PMDT) in India*. Central TB Division, Directorate General of Health Services, Ministry of Health & Family Welfare; 2012
7. Deun AV, Caminero JA. *How drug resistance affects tuberculosis treatment outcome and monitoring parameters. Guidelines for clinical and operational management of drug resistant tuberculosis*. 2013.
8. Snider Jr DE, Kelly GD, Cauthen GM, Thompson NJ, Kilburn JO. Infection and disease among contacts of tuberculosis cases with drug-resistant and drug-susceptible bacilli. *Am Rev Respir Dis*. 1985;132:125–132.
9. Burgos M, DeRiemer K, Small PM, Hopewell PC, Daley CL. Effect of drug resistance on the generation of secondary cases of tuberculosis. *J Infect Dis*. 2003;188:1878–1884.
10. Van Soolingen D, Borgdorff MW, de Haas PE, et al. Molecular epidemiology of tuberculosis in the Netherlands: a nationwide study from 1993 through 1997. *J Infect Dis*. 1999;180:726–736.
11. National action plan to combat multidrug-resistant tuberculosis. *MMWR*. 1992;41(RR-11):59–71.
12. Should we treat or follow contacts to MDR/XDR? *MMWR*. 1992;41(RR-11):59–71.

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: http://www.journals.elsevier.com/indian-journal-of-tuberculosis/

Original Article

Perspectives of health care provider regarding TB-HIV referral strategy and non-uptake of HIV testing in Delhi – A qualitative study

V.C. Soyam [a,*], N. Sharma [b], Jyoti Das [c], P. Boro [d], Charu Kohli [e], A. Khanna [f], G.S. Meena [b]

[a] Assistant Professor, MVJ Medical College and Research Hospital, Hoskote, Bangalore 562114, India
[b] Director Professor, Community Medicine Department, Maulana Azad Medical College, New Delhi, India
[c] Assistant Director, National Centre for Disease Control, New Delhi, India
[d] Senior Resident, Vardhaman Mahavir Medical College and Safderjang Hospital, New Delhi, India
[e] Senior Resident, Community Medicine Department, Maulana Azad Medical College, New Delhi, India
[f] Chief Medical Officer (SAG), DTO and In Charge Chest Clinic, Lok Nayak Hospital, New Delhi, India

ARTICLE INFO

Article history:
Received 6 October 2014
Accepted 8 July 2015
Available online 23 October 2015

Keywords:
DOTS provider
In depth interview
HIV testing

ABSTRACT

Background: DOTS provider and medical officer play an integral role in implementation of RNTCP. Understanding provider perspectives is an integral component of evaluating programme to improve services to identify the areas for quality improvement and universal HIV testing among TB patients.

Objective: To describe the perception of health care providers regarding TB-HIV referral strategy and reasons for non-uptake of HIV testing.

Methodology: A qualitative study was undertaken at DOTS cum microscopic centre of TB-Chest clinic of Lok Nayak Hospital and DOTS cum microscopic centre of rural area of west Delhi. In-depth interview of DOTS provider and medical officer in-charge at DOTS centre was conducted. A topic outline guide used to assess the perception of study subjects. Thematic analysis of qualitative data was done.

Results: The source of knowledge regarding HIV testing among DOTS providers were training and monthly review meetings. All the study participants knew the rational of HIV testing and the consequences of not being tested and are highly motivated for referring the patients for HIV testing at the earliest. Some of the barriers to HIV testing reported by the health care providers were lack of awareness, associated stigma, long distance travel by the patients and non-availability of HIV testing kits.

Conclusion: Health care providers were motivated for implementation of the strategy. Barriers to HIV TB testing strategy should be addressed.

* *Corresponding author*. Tel.: +91 9560945471.
E-mail address: drvish2004@gmail.com (V.C. Soyam).

http://dx.doi.org/10.1016/j.ijtb.2015.09.001

1. Introduction

Early identification of HIV (human immunodeficiency virus) in patients with TB (tuberculosis) is one of the key strategies to achieve TB-related millennium development goals.[1] Counselling and testing for HIV provide opportunities for prevention, treatment, care and support for HIV patients and is also a significant entry point to TB-HIV co-management.[2] Implementation of TB-HIV intensified package was started in Delhi in 2009, which includes routine referral of all TB patients for HIV counselling and testing, provision of CPT (Cotrimoxazole Preventive Therapy) to all HIV-TB co-infected patients and expanded recording and reporting including confidentiality.[3] As per RNTCP performance report 2010, despite the successful implementation of RNTCP in capital of India, Integrated Counselling and Testing Centre (ICTC) remains poorly utilized as only 58% registered patients knew their HIV status which is a matter of concern.[4] Therefore, Delhi State TB Department in collaboration with Delhi State AIDS Control Society (SACS) rolled out a new strategy in 2012 with improved cross referrals between ICTCs, Anti Retroviral Therapy (ART) Centres and RNTCP facilities to enable early initiation of ART and CPT. The strategy was implemented in Delhi with innovative interventions in the form of separately designed referral slips, strict quality control of records and combined monthly review meetings of RNTCP, ICTC and ART staff.[5] This has led to an increase in proportion of all registered TB cases with known HIV status to be approximately 80%.[6] Health care providers' knowledge, belief and practices play an important role in successful implementation of strategy of the programme.[7] Provider's beliefs have been reported as a barrier in a number of studies from different countries, such as Uganda, Tanzania and Ukraine.[8–10] Information from providers is intended to supplement and provide insights about HIV testing among TB patients. DOTS provider is uniquely positioned to understand and influence patients' behaviours.[11] Despite their influential position for TB patients, they have received very little attention in the literature to date.

Therefore, a study was planned to know providers' perspective regarding TB-HIV referral strategy and reasons for non-uptake of HIV testing.

2. Materials and methods

2.1. Study design, setting, sampling

A qualitative study was conducted at the urban DOTS cum microscopy centres under Chest Clinic of Lok Nayak Hospital, New Delhi, which is a tertiary care referral centre from January 2012 to February 2013. Two DOTS cum microscopy centres located in rural area, one at R.H.T.C. (Rural Health Training Centre) Barwala and other at MVH (Maharshi Valmiki Hospital) Pooth Khurd (field practice areas of Department of Community Medicine, Maulana Azad Medical College) were also included as study areas.

DOTS providers and medical officer centre in-charge of the selected DOTS centres constituted in the study population.

Those who were unwilling to participate in study were excluded from the study.

2.2. Methodology

In-depth interview of the DOTS provider and medical officer was conducted to know their perspective and knowledge regarding intensified package of TB-HIV and barriers in non-uptake of HIV testing among TB patients. Participants were approached at their work-place and asked for their willingness to participate in this study. Written informed consent was taken and interviews were conducted in a quiet place within the health care facility maintaining confidentiality.

Duration of interview varied between 30 and 45 min, focusing on the providers' perceptions on functioning of the intensified package of TB/HIV, social stigma for HIV/AIDS and TB, barriers to the programme and recommendations to improve the same. The interview was continued until no new information was coming from participants. The interviews were conducted in English or Hindi according to the health care providers' preference and were tape-recorded after obtaining consent. Recordings were listened again and again by team of two investigators and noted down the important points followed by consulted with the experts. Thematic analysis was done to know their perspectives regarding intensified package of TB-HIV, the importance of HIV testing in TB patients, approach for HIV testing by health care provider, barrier to HIV testing and suggestions to increase HIV testing. The results of the thematic analysis are as follows.

2.3. Results

Three medical officers and eight DOTS providers were included in the study. Out of eight DOTS providers, two were from rural area and six from the urban area. Mean age of DOTS providers was 35.1 ± 4.5 years of age. Six DOTS providers were males while two were females with average 6.5 ± 2.5 years of job experience. Of these respondents, 50% of them had heard the name of PITC (Provider Initiated HIV Testing and Counselling). All of them mentioned that, they were repeatedly told about the importance of HIV testing in TB patients during monthly meeting of DOTS provider by the DTO (District Tuberculosis Officer) and WHO consultants.

3. Perspective regarding intensified package of TB-HIV

3.1. DOTS providers

All DOTS providers knew about the intensified package of TB-HIV. The source of knowledge of the urban DOTS provider was mainly the review monthly meetings held with DTO and for the rural DOTS providers, there were in addition seminar/Continuous Medical Education (CME) held in district hospital (MVH, Pooth Khurd).

All of them said that according to intensified package of TB-HIV all TB patients must be referred to ICTC for HIV testing. Those found positive should be referred to ART centre to start

ART with CPT at the earliest so that TB-HIV patient can be managed effectively.

They all claimed that they were following the guidelines of the referral mechanism as per the intensified package of TB-HIV. They said that they followed the patients for their HIV status during their subsequent visit to DOTS centre if the patient did not get tested on their first encounter with them.

However, one of the urban DOTS providers admitted that he did not refer TB patients of age less than 5 years to ICTC, as he felt at that age one would not be at the risk of HIV infection unless there was a sign in the form of severe weakness or significant history.

Four (50%) DOTS providers said that the programme had increased awareness among TB patients about HIV/TB co-infection while two opined that in rural areas, many TB patients were still unaware of the relationship between the two diseases. Five of the eight DOTS providers graded the functioning of the TB-HIV programme as very good while two graded it as good and one as satisfactory. On asking whether their workload increased after introducing HIV testing for all TB patients all of the DOTS providers refused, except one who said that ''although a little paper work had increased, but the patients were being benefited from the same.''

3.2. *Medical officer*

Medical officer reported that TB-HIV intensified package was a welcome initiative being implemented in Delhi since 2009. Many patients were being benefited from this initiative since many patients were tested for HIV and receiving ART with CPT than before. All of them reported that functioning of the TB-HIV programme as very good. There has been an increase in the cross referral between these two programmes. All of them were trained in the TB-HIV intensified package.

4. Importance of HIV testing in TB patients

4.1. *DOTS providers*

All DOTS providers were aware of the relation of HIV/AIDS with TB. All agreed that it was necessary for every TB patient to be tested for HIV in order to identify TB/HIV co-infection early. All acknowledged that any patient found positive for HIV, must receive the ART to increase his/her survival. All reported that TB will not be cured if HIV co-infection is not addressed in the form of early initiation of ART. Three of them admitted that TB patients will acquire other opportunistic infections and the chances of mortality and morbidity would be increased if they were not started on CPT and ART. Two of them said that the HIV positivity is increasing among the TB patients; therefore, HIV testing among them is today's need. With the referral to ICTC clinic, all the TB patients were counselled regarding HIV/AIDS which also improve their knowledge regarding transmission and prevention of HIV irrespective of their HIV status.

4.2. *Medical officer*

All medical officers reported that HIV testing has been a significant entry point for TB patients. There was consensus in that all TB patients need to be tested for HIV as early as possible so that a patient can get access to ART and CPT. In a country like India, if a person gets infected by HIV, he/she will hardly come out themselves to undergo HIV testing until the opportunistic infections manifest. As TB is the first opportunistic infection in our country because of high burden, all TB patients must be screened for HIV at the earliest. One stated that TB and HIV have a synergistic effect on each other, and one of them if missed out then the, missed infection will accentuate the other.

5. Approach to HIV testing

5.1. *DOTS providers*

Although all DOTS providers offered HIV testing to all the TB patients, they said that they did not explain the name of the test to majority of them. They elaborate it only, if any patient asks for what they have been referred to and show interest to know about HIV. On asking when they refer TB patients to HIV testing, all answered that they refer all the TB patients on the same day with referral form provided to them except one female DOTS provider who admitted that very few times she used to write for HIV test on patients TB treatment card. All the providers said that they were practicing to keep the referral form with them in a separate file and mentioned the result of HIV testing on TB treatment card provided to them. If any patient was found to be not tested for HIV on their subsequent visit, then they ask the reason of non-uptake and again refer them to ICTC. Five out of the eight providers reported that they never encountered any TB patient refusing to get tested for HIV. Three providers mentioned that if any patient refuses, then they send the patient to the doctor for counselling or provide the information themselves regarding TB-HIV co-infection. Two of them mentioned that in those patients who did not undergo testing even after 3 or 4 visits, they stop asking them for testing again. Six out of eight DOTS providers said that they try to get the HIV status of their patients within a week of initiation of TB treatment, while two of them set the target of 10 days.

5.2. *Medical officers*

All officers said that they review the monthly progress of their DOTS centre in which they enquire from each DOTS provider about how many patients were referred to ICTC, how many tested out of them, number of positive patients and whether all positives were referred to ART centre for further management. They instructed all the doctors that if they suspect any patient for TB then they should refer the patient for HIV testing along with the work up for TB diagnosis.

6. Barriers to HIV testing

6.1. *DOTS provider*

Major barrier reported by the DOTS provider was the long distance between DOTS and ICTC. Three of the DOTS providers

said that those who were employed were likely to get tested at a later date than those who were unemployed. Two of them also noticed that students also get tested late due to the coincidental timings of their school/college and ICTC. Some of responses are: ''If we tell somebody to be tested for AIDS, they get offended''. ''They think we suspect them to be immoral. Many are not aware of other modes of transmission of the disease. More awareness programs are essential. Some people in rural areas do not know what AIDS is''.

6.1.1. *Stigma for HIV/AIDS and TB*

Social stigma for HIV/AIDS was identified by six of the eight health care providers as a huge barrier to this programme. According to them, stigma for HIV/AIDS was more than the stigma for TB. Other two health care providers identified social stigma for both HIV/AIDS and TB as barriers that prevented many patients from seeking timely care.

> ''Stigma is a major obstacle for the program. Some adolescent girls say 'we came to be treated for TB, not for HIV testing'. Many a times parents do not prefer their children to be tested, because they think that they were not at risk or it was not necessary to be tested or they fear blood test. Stigma for HIV is more than for TB''.

6.1.2. *Lack of adequate pre and post HIV-testing counselling*

Two health care providers reported that the present HIV counselling services were inadequate and that patients were not fully aware of the implications of HIV testing.

> ''Counselling should be improved. Some HIV positive patients are not aware of their HIV status even after post-test counselling and ask me what disease they have....'' (Rural DOTS Provider)

One of the health care providers felt that some TB patients agreed for HIV testing because of the authoritative position of health workers and for the fear of not receiving good care if they did not comply.

> ''Illiterate and old people are not aware of what is AIDS. They undergo testing because the DOTS provider or doctor told them to do. Some think they will not receive good care if they do not do the test.''

6.1.3. *Lack of HIV testing kits*

Three of the health care providers opined that the lack of regular supply of HIV testing kits was an important barrier to the integrated HIV/TB programme.

> ''We are getting more TB patients now for HIV testing. Sometimes there is shortage of kits and TB patients get angry, if we ask them to bring the HIV test result on subsequent visit'' (Rural DOTS Provider)

6.2. *Medical officers*

All of them reported that majority of TB patients enrolled in their chest clinics are being tested for HIV. One of them further said that very few subjects are not being tested for HIV those who are less than 2 years of age and those who are not able to walk or are very sick. Senior officers also raised the same issue of shortage of HIV kits.

7. Suggestions to increase HIV testing

7.1. *DOTS providers*

All health care providers agreed that awareness about HIV/AIDS and HIV/TB co-infection must be increased to improve the uptake. All the DOTS providers suggested that long distance of ICTC from DOTS centre needs to be addressed. Long queue in ICTC also makes the already sick TB patients disinterested to get tested and the chances of spread of TB to other clients would be increased. Hence TB patients should get first priority for testing. Five DOTS providers noticed that as patients have to visit ICTC two to three times to complete the whole procedure, it is also a de-motivating factor for TB patients.

7.2. *Medical officers*

All medical officers suggested that there should be proper training of DOTS providers. ''We almost achieve the quantity of care but we are still lacking in providing the quality of care to TB patients''. One DTO suggested that we need more trained DOTS providers and counsellors to address the patient–provider communication gap. Two of them opined that regular meetings between HIV and TB care providers are necessary for improving the functioning of this programme.

> ''Regular meetings between RNTCP staff and ICTC staff are essential. Problems can be discussed and resolved in these meetings...''

Two of the officers also proposed that there should be an uninterrupted supply of HIV kits and the government should take care of it.

8. Discussion

The present study offers insight into DOTS providers' and medical officers perspectives regarding TB-HIV intensified package in a specific context. We sought to find out perception of providers for non-uptake of HIV testing in TB patients by doing in depth interviews of 8 DOTS providers and 3 medical officers. All the providers reported that they were aware that all TB patients have to be referred for HIV testing except one who considered that less than 5-year-old child is not at a risk. However a study done by Bishnu et al. in West Bengal district revealed that more than half of providers reported awareness of the policy to refer all patients with TB for HIV testing.[7] The reason for higher level of awareness in present study could be due to training and regular monthly review meeting for sensitization of DOTS providers. Almost all providers believed that TB patients accept and simultaneously undergo the HIV test when they offer it. They reportedly followed the practice of

offering HIV test on subsequent visits if the patient was not tested at the first visit. In contrast to this, a study from West Bengal reported that almost all providers believed that patients would not undergo HIV testing even when recommended by a provider.[7] The reason that providers gave for this were that: ICTCs were not co-located with TB facilities, were too far for patients to travel especially in view of poor public transport facilities, and that ICTCs provided irregular services and frequently suffered from HIV testing kit shortages. In contrast to this, present study showed that DOTS providers' perspective though similar to West Bengal study that the distance between ICTC and DOTS centre was long and also that sometimes HIV kit was not available at ICTC, they still referred almost all TB patients.[7] Study from Uganda also revealed logistical shortages similar to present study.[8] Another qualitative study from Zimbabwe also pointed out the shortage of appropriate counselling space and shortages of HIV test kits were the main challenges.[11]

Providers in the West Bengal felt that very few patients were likely to be HIV positive and therefore they questioned the rationale for referring all patients for testing.[7] However, in the present study, providers mentioned that although HIV positivity among TB patients are less, still all TB patients should be referred for HIV testing. From the in-depth interviews of providers and after comparing with the qualitative study of West Bengal, it can be concluded that DOTS providers of this study were more knowledgeable and highly motivated. This could be due to regular monthly meetings and constant supervision from senior officers.[7]

All providers were aware of the rationale of referring TB patients for HIV testing and all opined that it was necessary for each TB patient to be tested for HIV in order to identify TB/HIV co-infection early.

Regarding approach to HIV testing in TB patients, all providers admitted that they refer all the patients on same day whenever possible, but they do not mention the name of test to patients unless he/she asks. Therefore it is suggested that there is gap in the policy implementation.

In a study conducted by Anuwatnonthakate et al. in Thailand, it was observed that providing HIV testing directly in TB clinics, rather than in other settings, may increase the proportion of TB patients with known HIV status.[14] Stigma related to TB as well as for HIV is huge in India as reported by DOTS provider and also by medical officers. A study of South Africa done by Heunis et al. also reported similar finding. Fear of stigmatization as a reason for TB patients' non-uptake of HIV testing also featured prominently in the findings of a qualitative study in Durban, South Africa by Daftary et al. in 2007.[15] Poor patient–provider communication was identified as barrier for HIV testing by medical officers in our study. Similarly in a study of Mahendradhata et al., the programme managers perceived poor patient–provider communication as one of the most influential barriers to acceptance of HIV testing.[16]

9. Conclusion

Most of the DOTS providers referred all TB patients to ICTC for HIV testing as early as possible. They were all aware about the rationale of referring TB patients for HIV testing. The long distance between DOTS centre and ICTC, patients not able to walk and non-availability of kits were the major barriers to HIV testing identified by health care providers. There is a need to address the barriers reported by medical officers and DOTS providers to improve the uptake of HIV testing among TB patients. Suggestion given by provider can be implemented on pilot basis.

Conflicts of interest

The authors have none to declare.

Acknowledgements

Our sincere acknowledgement goes to Department of Community Medicine, Maulana Azad Medical College, and New Delhi for the opportunity we had to conduct this study. Gratitude is also deeply expressed to Guide and Co-guide for their valuable guidance. DOTS providers and medical officers are appreciated for their interest and full participation shown in the study.

REFERENCES

1. Ayenew A, Leykun A, Colebunders R, Deribew A. Predictors of HIV testing among patients with tuberculosis in North West Ethiopia: a case–control study. *PLoS ONE*. 2010;5(3):e9702.
2. Kigozi NG, Heunis JC, Chikobvu P, van den Berg H, van Rensburg HCJ, Wouters E. Predictors of uptake of human immunodeficiency virus testing by tuberculosis patients in Free State Province, South Africa. *Int J Tuberc Lung Dis*. 2010;14(4):399–405.
3. *National Framework for Joint HIV/TB Collaborative Activities October 2009*. Delhi: CTD, NACO and MOHFW; 2011. 29 pp. Available from http://www.tbcindia.org. Accessed 29.06.11.
4. *RNTCP Performance Report 2010*. Delhi: State TB Cell; 2011. Available from http://www.Dotsdelhi.org/newsletter2011.php. Accessed 28.06.11.
5. Gupta AK, Singh GP, Goel S, Kaushik PB, Joshi BC, Chakraborty S. Efficacy of a new model for delivering integrated TB and HIV services for people living with HIV/AIDS in Delhi – case for a paradigm shift in national HIV/TB cross-referral strategy. *AIDS Care*. 2014;26(February (2)):137–141.
6. *TB India 2014*. Central TB Division. Available from http://www.tbcindia.nic.in/pdfs/TB%20INDIA%202014.pdf. Accessed 12.01.15.
7. Bishnu B, Bhaduri S, Kumar AMV, et al. What are the reasons for poor uptake of HIV testing among patients with TB in an Eastern India District? *PLoS ONE*. 2013;8(3):e55229. http://dx.doi.org/10.1371/journal.pone.0055229.
8. Okot-Chono R, Mugisha F, Adatu F, Madraa E, Dlodlo R, Fujiwara P. Health system barriers affecting the implementation of collaborative TB-HIV services in Uganda. *Int J Tuberc Lung Dis*. 2009;13(8):955–961.
9. Wandwalo E, Kapalata N, Tarimo E, Corrigan CB, Morkve O. Collaboration between the national tuberculosis programme and a non governmental organisation in TB/HIV care at a

district level: experience from Tanzania. *Afr Health Sci*. 2004;4:109–114.
10. Van der Werf MJ, Yegorova OB, Chechulin Y, Hasker E, Veen J, Turchenko LV. HIV testing practices of TB patients after introduction of a new testing policy in Kiev City, Ukraine. *Int J Tuberc Lung Dis*. 2005;9:733–739.
11. Heunis JC, Wouters E, Norton WE, et al. Patient- and delivery-level factors related to acceptance of HIV counseling and testing services among tuberculosis patients in South Africa: a qualitative study with community health workers and program managers. *Implement Sci*. 2011;6:27.
14. Anuwatnonthakate A, Jittimanee SX, Cain J, et al. Barriers to human immunodeficiency virus testing of tuberculosis patients in Thailand, 2004–2007. *Int J Tuberc Lung Dis*. 2010;14 (8):980–985.
15. Daftary A, Padayatchi N, Padilla M. HIV testing and disclosure: a qualitative analysis of TB patients in South Africa. *AIDS Care*. 2007;19(4):572–577.
16. Mahendradhata Y, Andono Ahmad R, Lefèvre P, Boelart M, Van der Stuyft P:. Barriers for introducing HIV testing among tuberculosis patients in Jogjakarta, Indonesia: a qualitative study. *BMC Public Health*. 2008;8:385.

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: http://www.journals.elsevier.com/indian-journal-of-tuberculosis/

Original Article

Oral health status and awareness among tuberculosis patients in an Indian population

Payal Saxena [a], *Saurabh Kumar Gupta* [a,*], *Atul Kharate* [b], *S.V.S. Prasad* [c], *Abhishek Maurya* [d], *Parul Saxena* [e], *Shivam Kamthan* [e]

[a] *Assistant Professor, Government College of Dentistry, Indore, Madhya Pradesh, India*
[b] *Director, Manorama Raje TB Hospital, Indore, Madhya Pradesh, India*
[c] *Senior Scientist, Indian Agricultural Research Institute – Regional Station, Indore, Madhya Pradesh, India*
[d] *Intern, Government College of Dentistry, Indore, Madhya Pradesh, India*
[e] *Resident, Hindu Rao Hospital, Malkaganj, New Delhi, India*

ARTICLE INFO

Article history:
Received 24 April 2014
Accepted 8 July 2015
Available online 9 October 2015

Keywords:
CPI score
Periodontal health
Tooth pain
Gum bleeding

ABSTRACT

Background: Knowledge and awareness regarding oral health problems of tuberculosis patients are lacking among patients, physicians, as well as dental practitioners.
Aim: This study aimed to assess the oral health status and awareness among the tuberculosis patients in an Indian population.
Methods: Study sample comprised of 210 tuberculosis patients and 210 nontuberculosis subjects. The tuberculosis patients were categorized into new patients (group A), previously treated (group B), and drug-resistant tuberculosis patients (group C). History of present problem and awareness about oral health was noted. Periodontal health status was ascertained using Community Periodontal Index (CPI). Other oral findings were also recorded.
Results: The results were analyzed statistically. 62.9% of total tuberculosis patients had one or more oral problems. Most common problem was tooth pain (34%). CPI score was significantly higher ($p < 0.05$) for tuberculosis patients (2.94) than in control group (1.34). Mean CPI score for groups A, B, and C patients was 2.83, 2.91, and 3.09, respectively.
Conclusion: This study suggests awareness of oral health status and oral manifestations of tuberculosis among physicians and dental professionals.

1. Introduction

Tuberculosis is a major global health accounting for a major bulk of the affected population. Even after the availability of effective drugs and vaccines, making it a preventive and curable disease, it remains a worldwide health issue being the second most common cause of death from an infectious disease, after the human immunodeficiency virus (HIV). The emergence of drug resistance forms together with its association with HIV has led to a more critical situation.[1]

* *Corresponding author at*: Department of Conservative Dentistry and Endodontics, Government College of Dentistry, Sardar Patel Marg, Indore, Madhya Pradesh, India. Tel.: +91 0731 4278545; fax: +91 731 2701608; mobile: +91 8103078123.
E-mail address: payal.endo@gmail.com (S.K. Gupta).
http://dx.doi.org/10.1016/j.ijtb.2015.09.002

Oral manifestations of the tuberculosis are rare, despite being important. There have been studies and various case reports published[2–6] with reference to the oral lesions as being primary or secondary manifestation of the disease, but literature is very limited in relation to the oral health status of such patients. In developing countries such as India, where the low-income population becomes a primary target of the disease, the oral health is largely neglected but adds to the morbidity of the patient. The purpose of the present study was to document the oral health problems and to access the oral health status and awareness among the patients suffering from tuberculosis in an Indian population.

2. Study population and methods

2.1. Sample selection

The study population comprised 210 tuberculosis patients (119 male, 91 female) between 18 and 70 years of age (mean 33.64 years) visiting the Government tuberculosis and chest hospital, Indore, Madhya Pradesh, India. This being a specialty Tuberculosis Center, a representative section of the society comprising of all the ethnic and cultural groups attended the same. The control group consisted of 210 age- and sex-matched nontuberculosis patients randomly drawn from volunteers visiting the dental camps on ten primary locations of same territory. Care was taken to include approximately equal representation from both sexes and as many cultural backgrounds as possible.

Inclusion criteria for both the study and the control group were patients with at least 20 teeth present in the mouth and aged between 18 and 70 years. Informed written consent was obtained from all the participants in this study.

Tuberculosis patients were categorized on the basis of history of previous tuberculosis treatment (patient registration group) according to WHO guidelines[6] into groups A and B, and drug-resistant patients were included in group C as follows:

- **Group A**: *New patients* have never been treated for tuberculosis or have taken anti-tubercular drugs for less than 1 month.
- **Group B**: *Previously treated patients* have received 1 month or more of anti-tubercular drugs in the past including relapse patients, treatment after failure patients and treatment after loss to follow-up patients.
- **Group C**: All drug resistance tuberculosis patients.

2.2. Questionnaire

All relevant information regarding the age, gender, education, BCG vaccination history, awareness about oral hygiene (cleaning of teeth, visit to dentist), oral hygiene aids used (finger, stick, tooth brush, tooth paste, tooth powder, tongue cleaner), frequency of tooth brushing (once, twice daily), tobacco use, awareness of cancer due to tobacco use, details of oral problem (if present), and any other medical condition were recorded. Detailed history regarding tuberculosis disease (previous and present symptoms, earlier medication) was also noted.

2.3. Clinical examination

Clinical examination of oral cavity was done by experienced dentists (SKG, PS, AM) for oral hygiene status, any ulcer or other finding. Periodontal status assessment was done with a Community Periodontal Index (CPI) probe (Hu-Friedy, Chicago, IL, USA), with a 0.5 mm ball tip, with a black band between 3.5 and 5.5 mm. The teeth examined were 17, 16, 11, 26, 27, 37, 36, 31, 46, and 47. Although 10 index teeth were examined and only the highest score relating to each sextant was made. The CPI was recorded for the study and the control group.

Clinical examination for tuberculosis and related symptoms was done by a specialist (AK) and a general physician (PS).

2.4. Statistical analysis

Statistical analysis was done using SPSS (10.0) statistical software. Statistical tests employed for the obtained data in our study were Fischer test, *Z* test, and Mann–Whitney *U* test.

3. Results

Table 1 shows distribution of tuberculosis patients according to age, gender, education, vaccination, presence of oral problem, oral hygiene practices, visits to dentists, use and awareness for tobacco, and presence of other disease. 62.9% of total tuberculosis patients complained of one or more oral

Table 1 – Demographic details and assessment of oral health awareness among tuberculosis patients (n = 210).

Age in years; average (max–min)	33.64 (13–70)
Gender	Male 56.7%, female 43.3%
Education	Illiterate 44.3%, primary 31.4%, high school 20.5%, degree 3.8%
BCG vaccinated patients	93 (44.3%)
Oral problem present	132 (62.9%)
Common oral problem present	Tooth pain 45 (34%), gum bleeding 43 (32.6%), sensitivity 20 (15.2%), food impaction 14 (10.6%)
Cleaning method	Brush 92 (43.8%), wooden stick (datun) 6 (2.9%), finger 32 (15.2%), none 2 (1%)
Dentifrice	Paste 144 (68.6%), powder 55 (26.2%), none 9 (4.2%)
Visit to dentist	Never 177 (84.3%), on problem 33 (15.7%)
Tobacco use	102 (48.6%)
Tobacco awareness	77 (36.7%)
Frequency of teeth cleaning	Once 195 (92.9%), twice 13 (6.2%), never 2 (1%)
Frequency of tongue cleaning	Daily 45 (21.4%), never 146 (69.5%), rarely 19 (9%)
Other findings	HIV 16 (7.62%), SMF 10, lymph node enlargement 36 (17.1%), oral ulcer 6 (2.9%)

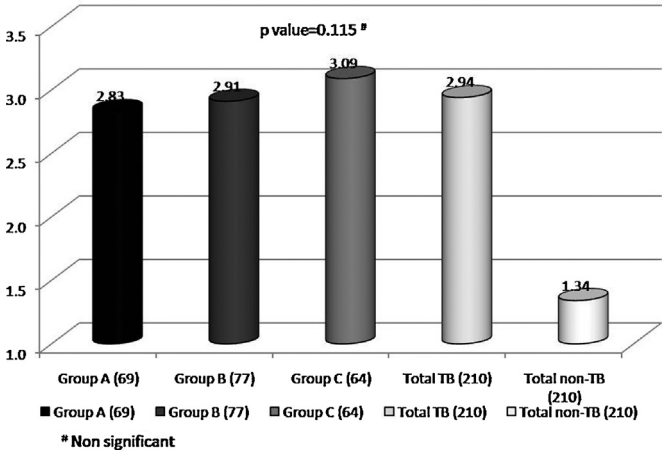


Fig. 1 – Mean Community Periodontal Index scores of different categories.

problems. Most common complaint was tooth pain (34%) followed by gum bleeding (32.6%), sensitivity (15.2%), and food impaction (10.6%). 84.3% of total tuberculosis patients had never visited to dentist. 48.6% (102) consumed tobacco, out of which 43 (42.15%) were aware of ill-effects of tobacco. 92.9% (195) of total patients used to brush once a day, 6.2% (13) twice a day, and 1% (2) never brushed at all. 69.5% (146) patients had never cleaned their tongue.

CPI score of total tuberculosis patients (210) was 2.94 in comparison to 1.34 of control group (210). This difference was statistically significant ($p < 0.05$; Table 1). On intra group comparison among tuberculosis patients, interestingly, with the advancement of chronicity and drug-resistance of disease, the severity of periodontal disease also increased. Mean CPI score for groups A, B, and C patients was 2.83, 2.91, and 3.09, respectively, although this difference was statistically insignificant ($p > 0.05$; Fig. 1).

Periodontal examination was carried out on all the teeth and each sextant was compared, as this would avoid underemphasis/overemphasis. Periodontal status of both tuberculosis and nontuberculosis patients is depicted in Table 2. It was found that CPI scores representing periodontal status were significantly higher in both the sexes among tuberculosis patients in comparison to nontuberculosis control group ($p < 0.05$; Table 2).

On comparing various locations in oral cavity (sextant-wise distribution), the difference was highly significant among the tuberculosis patients in all sextants in comparison to control ($p < 0.05$; Table 2 and Fig. 2). Mandibular right side was most affected followed by maxillary left, mandibular anterior, mandibular left, maxillary right, and maxillary anterior sextants.

Other oral findings included oral ulcers in 6 (2.9%), sub mucous fibrosis in 10 (4.76%), and generalized attrition in 18 (8.57%) patients. 16 (7.62%) patients were having HIV infection. Lymph node enlargement was seen among 36 (17.1%) patients (Table 1).

4. Discussion

Despite the encouraging progress of tuberculosis control programs, the global burden of tuberculosis remains enormous. Geographically, South-East Asia and Western Pacific regions accounted for 60% of cases globally. India alone is having 26% of worldwide cases.[1] There is still a lack of stress on oral health by the authorities for tuberculosis patients. Previous studies[2–6] have mainly focused on oral ulcers or growth as the primary manifestation of tuberculosis, periodontal health status of the patients has been largely neglected. To the best of our knowledge, assessment of periodontal health of tuberculosis patients in Indian population is limited. As suggested by this study, there is increased CPI score (2.94); that is indicative of significantly compromised periodontal health of tuberculosis patients in comparison to control group (CPI score, 1.34). 62.9% of total tuberculosis patients were suffering from one or more oral problems. It can be safely concluded that severity of periodontal disease among tuberculosis patients is also dependent on advancement and drug-resistance of disease. Drug-resistant tuberculosis patients were having higher mean CPI score (3.09) in comparison to previously treated (2.91) followed by new patients. On basis of this study, a direct cause–effect relationship between tuberculosis and compromised periodontal health can be suggested. Furthermore specific studies will be required to confirm this relationship.

Table 2 – Comparative periodontal status (CPI scores) of tuberculosis and nontuberculosis patients at different sextant of dental arch.

Groups	Maxillary right	Maxillary anterior	Maxillary left	Mandibular right	Mandibular anterior	Mandibular left	CPI score
Male TB (119)	2.14 ± 1.27	1.66 ± 1.07	2.41 ± 1.13	2.63 ± 1.02	2.35 ± 1.01	2.29 ± 0.86	2.95 ± 0.81
Male non-TB (105)	0.95 ± 0.66	0.68 ± 0.61	1.0 ± 0.73	0.95 ± 0.73	0.92 ± 0.69	1.01 ± 0.83	1.35 ± 1.00
p Value	0.000	0.000	0.000	0.000	0.000	0.000	0.000
Female TB (91)	2.18 ± 1.22	1.60 ± 1.10	2.41 ± 1.13	2.54 ± 0.96	2.19 ± 0.95	2.13 ± 0.87	2.92 ± 0.76
Female non-TB (95)	0.86 ± 0.69	0.58 ± 0.56	0.94 ± 0.67	0.99 ± 0.74	0.86 ± 0.71	0.99 ± 0.72	1.32 ± 0.93
p Value	0.000	0.000	0.000	0.000	0.000	0.000	0.000
Total TB (210)	2.17 ± 1.22	1.64 ± 1.10	2.41 ± 1.13	2.61 ± 0.96	2.30 ± 0.95	2.25 ± 0.87	2.94 ± 0.76
Total non-TB (210)	0.91 ± 0.67	0.63 ± 0.59	0.97 ± 0.70	0.97 ± 0.73	0.90 ± 0.70	1.0 ± 0.77	1.34 ± 0.96
p Value	0.000	0.000	0.000	0.000	0.000	0.000	0.000

p Value < 0.05 = HS.

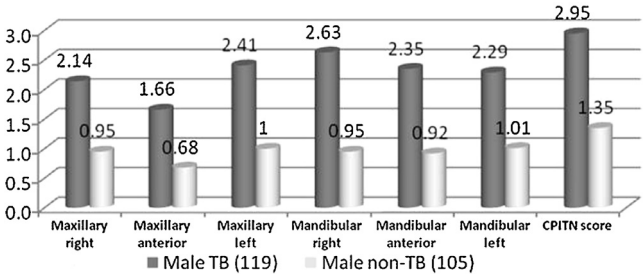


Fig. 2 – Mean Community Periodontal Index scores of tuberculosis and nontuberculosis male patients at different sextant of dental arch.

Population-based studies have identified a number of risk factors including age, male gender, tobacco consumption, HIV co-infection, diabetes, anemia, drug resistance, disease severity as co-morbid conditions following a diagnosis of tuberculosis.[7–11] HIV infection was the most common co-morbid condition among tuberculosis patients in this study. The percentage of tuberculosis patients with HIV was 7.62%. This is in accordance with the WHO report, which estimated HIV prevalence among tuberculosis patients in India to be 8.6%.[12] Patients (48.6%) had the habit of tobacco consumption, which could have been avoided or rather the Government should have prohibited, for both better prognosis of disease and oral health.

With respect to presence of oral ulcers, 2.9% (6) of the patients had oral ulcer. This is higher than previous studies[13,14] reporting from 0.8% to 1%. In our study, all the oral ulcers were secondary to lung involvement as previous studies.[14,15] Among other oral findings, sub mucous fibrosis (4.76%) and generalized attrition (8.57%) were common. 17.1% patients had either cervical or submandibular lymph node enlargement. Conclusively, recent increase in the incidence of tuberculosis, combined with an emerging global resistance to anti-tubercular drugs, warrants an amplified awareness of the involvement of *Mycobacterium tuberculosis* in persistent or atypical lesions in the oral cavity as well as compromised oral health status of these patients. Therefore, it becomes the responsibility of the dental professionals and physicians to be aware of the oral health status and oral manifestations of tuberculosis. On the basis of results of this study, it can be suggested that regular oral health check-ups should be a requisite for all tuberculosis patients. Simple oral hygiene measures should be prescribed along with proper management of present oral problems.

Conflicts of interest

The authors have none to declare.

REFERENCES

1. World Health Organization (WHO). *Global tuberculosis report*. 2012 Available from: *www.who.int/iris/bitstream/10665/75938/1/9789241564502_eng.pdf* [accessed 06.08.13].
2. Verma S, Mohan RP, Singh U, Agarwal N. Primary oral tuberculosis. *BMJ Case Rep*. 2013;1(August). http://dx.doi.org/10.1136/bcr-2013-010276.
3. Aggarwal P, Saxena S, Reddy V, Sharma P, Aggarwal V. Tuberculosis, the culprit behind nonhealing oral lesions: report of two cases. *Indian J Med Sci*. 2012;66(11–12):280–285.
4. Javali MA, Patil V, Ayesha H. Periodontal disease as the initial oral manifestation of abdominal tuberculosis. *Dent Res J (Isfahan)*. 2012;9(5):634–637.
5. Sharma P, Saxena S, Aggarwal P, Reddy V. Tuberculosis of odontogenic cyst. *Indian J Tuberc*. 2013;60(1):50–54.
6. World Health Organization (WHO). *Definitions and reporting framework for tuberculosis*. Geneva: WHO; 2013 Available from: *http://apps.who.int/iris/bitstream/10665/79199/1/9789241505345_eng.pdf* [accessed 06.08.13].
7. Alavi-Naini R, Moghtaderi A, Metanat M, Mohammadi M, Zabetian M. Factors associated with mortality in patients with tuberculosis. *J Res Med Sci*. 2013;18(1):52–55.
8. Khan K, Campbell A, Wallington T, Gardam M. The impact of physician training and experience on the survival of patients with active tuberculosis. *Can Med Assoc J*. 2006;175:749–753.
9. Pablos-Mendez A, Sterling TR, Frieden TR. The relationship between delayed or incomplete treatment and all-cause mortality in patients with tuberculosis. *J Am Med Assoc*. 1996;276:1223–1228.
10. Anyama N, Bracebridge S, Black C, Niggebrugge A, Griffin SJ. What happens to people diagnosed with tuberculosis? A population-based cohort. *Epidemiol Infect*. 2007;135:1069–1076.
11. Manosuthi W, Kawkitinarong K, Suwanpimolkul G, et al. Clinical characteristics and treatment outcomes among patients with tuberculosis in Bangkok and Nonthaburi, Thailand. *Southeast Asian J Trop Med Public Health*. 2012;43(6):1426–1436.
12. *Global tuberculosis control: WHO report*. 2011 http://whqlibdoc.who.int/publications/2011/9789241564380_eng.pdf.
13. Kumar PM, Kumar SM, Sarkar S, Ramasubramanian S, Anu KJ, Aravindh L. Oral manifestations in patients with pulmonary tuberculosis. *Int J Biol Med Res*. 2012;3(2):1565–1567.
14. Santiago RA, Gueiros LA, Porter SR, Gomes VB, Ferrer I, Leão JC. Prevalence of oral lesions in Brazilian patients with tuberculosis. *Indian J Dent Res*. 2013;24(2):245–248.
15. Komet H, Schaefer RF, Mahoney PL. Bilateral tuberculous granulomas of the tongue. *Arch Otolaryngol*. 1965;82:649–651.

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: http://www.journals.elsevier.com/indian-journal-of-tuberculosis/

Original Article

Thyroid profile status of patients treated for multidrug-resistant tuberculosis in state of Meghalaya, India

Gautom Kumar Saharia [a,*], *Alice Abraham Ruram* [b], *Joyantimon Lyngwa* [c]

[a] *Senior Resident, Department of Biochemistry, Post Graduate Institute of Medical Education and Research (PGIMER), Chandigarh 160012, India*

[b] *Associate Professor, Department of Biochemistry, North Eastern Indira Gandhi Regional Institute of Health and Medical Sciences (NEIGRIHMS), Shillong, Meghalaya, 793018, India*

[c] *District Tuberculosis Officer, District TB Centre, East Khasi Hills District, Jhalupara, Shillong, 793002, India*

ARTICLE INFO

Article history:
Received 18 August 2014
Accepted 8 July 2015
Available online 9 October 2015

Keywords:
Multidrug-resistant tuberculosis (MDR-TB), DOTS Plus
Hypothyroidism
Meghalaya

ABSTRACT

Background: Meghalaya has high tuberculosis burden with increasing multidrug-resistant tuberculosis (MDR-TB) cases. Drug-induced hypothyroidism is one of the well-documented adverse effects in treatment of MDR-TB, the data of which are unavailable in the population residing in this part of the Indian subcontinent.

Aim: This study was undertaken to assess the thyroid profile status of patients under DOTS Plus treatment and to evaluate the effects of anti-tubercular drugs on thyroid functions with respect to the pre-treatment thyroid status.

Methods: A prospective study of 114 patients who initiated treatment for MDR-TB between June 2012 and August 2013 was performed. Thyroid hormones, viz., TSH, Total T3, Total T4, Free T3 and Free T4 were estimated.

Results: Out of our study group of 114 MDR-TB patients, 15 dead patients and defaulters were excluded. So, out of 99 patients, till now, 76 patients have completed 6 months of DOTS Plus treatment and were re-evaluated for thyroid status. 52(68%) patients showed TSH levels more than the reference limit of 5.60 μIU/mL and 5(7%) patients had TSH >10 μIU/mL suggesting presence of sub-clinical hypothyroidism.

Conclusion: We suggest the need for Mandatory TSH screening at baseline and then six months interval for all patients taking DOTS Plus so that no adverse effect goes under-reported and early intervention if required should be done to maintain proper adherence.

* *Corresponding author at*: 4C Neelkamal Enclave, Jatia, Kahilipara Main Road, PO: Assam Sachivalaya, Guwahati, Assam 781006, India. Tel.: +91 9864440087.

E-mail address: gsaharia@yahoo.com (G.K. Saharia).

http://dx.doi.org/10.1016/j.ijtb.2015.09.003

1. Introduction

India is the highest tuberculosis (TB) burden country accounting for one-fifth (21%) of the global incidence. An increasing morbidity and mortality from TB in the near future is forecast for the world at large, with the number of newly occurring cases predicted to increase from 7.5 million a year in 1990 to 8.8, 10.2 and 11.9 million in the years 1995, 2002 and 2005, respectively, an increase amounting to 58.6% over a 15-year period.[1] For the year 2012, the incidence and prevalence of TB in India are 168 and 232, respectively per lakh population.[2] During this period, the incidence and prevalence of TB in the state of Meghalaya are 170 and 188, respectively per lakh population[3] showing a higher than national incidence rate. Moreover, the association with HIV and increasing multidrug-resistant tuberculosis (MDR-TB) is becoming a serious issue, especially for the developing nations like India.

Although major progress has been made towards achieving global control of tuberculosis (TB) over the past two decades, this progress is being threatened by M/XDR-TB, a form of TB that is more difficult and costly to diagnose, treat and cure than drug-susceptible TB. MDR-TB is defined as resistance to at least isoniazid and rifampicin (two of the most potent first-line anti-TB drugs), with or without resistance to other first-line drugs. MDR-TB is important because patients with this type of drug resistance respond extremely poorly to standard anti-TB treatment with first-line drugs. MDR-TB requires relatively costly laboratory diagnosis and treatment for at least 2 years with drugs that are expensive, toxic and not particularly potent. A case of MDR-TB is about 20–40 times more expensive to manage than a case of drug-sensitive TB and patient suffering is magnified with an impact on the economy of the country. In 2008, the World Health Organization (WHO) estimated that 440,000 cases of MDR-TB emerged globally; 85% of its global burden occurs in 27 countries.[4] Globally, 3.6% of new TB cases and 20.2% of previously treated cases are estimated to have MDR-TB. These estimates are essentially unchanged from 2011.[5] India is also no exception with a prevalence of MDR-TB to be ~3% among new TB cases and 12–17% among previously treated TB cases.[6] These surveys have been used by WHO in the Global TB Report 2011, which estimated, among the 1.5 million RNTCP-notified cases of pulmonary TB in India in 2010, approximately 64,000 cases of MDR-TB that could be diagnosed. India initiated the DOTS Plus strategy under the Revised National Tuberculosis Control Programme (RNTCP) for the MDR-TB patients with effect from August 2007. Here, standardized treatment regimen for MDR-TB under daily DOT includes 6–9 months of Kanamycin, Levofloxacin, Cycloserine, Ethionamide, Pyrazinamide and Ethambutol in the intensive phase and then 18 months of Levofloxacin, Cycloserine, Ethionamide and Ethambutol in the continuation phase. PAS is used as a substitute drug in case of intolerance. It is already known that these second-line drugs under Cat-IV used for treatment of MDR-TB have a number of adverse effects involving almost every system of the body and hypothyroidism is one of them, which is a well-documented, but relatively uncommon and often overlooked adverse effect. In the East Khasi Hills (EKH) district of Meghalaya, treatment under DOTS Plus started from June 2012. But till now no such data are available regarding the adverse effects of these drugs on the thyroid gland of the population residing in this part of the Indian subcontinent. Keeping all these facts in mind, we have decided to carry out a prospective study amongst all the patients under DOTS Plus treatment in EKH district of Meghalaya with the objectives of assessing the thyroid profile of MDR-TB patients under DOTS Plus treatment and to evaluate the effects of anti-tubercular drugs on thyroid functions with respect to the pre-treatment thyroid status of MDR-TB patients as most of these MDR-TB patients live in resource-poor and geographically difficult settings where laboratory screening may not be readily available, and side effects may go undiagnosed.

2. Material and methods

2.1. Study design and setting

The present study was undertaken in the Clinical Chemistry Laboratory of Department of Biochemistry, North Eastern Indira Gandhi Regional Institute of Health and Medical Sciences (NEIGRIHMS), Shillong in collaboration with District TB Office, EKH District, Shillong, Meghalaya. This prospective and longitudinal study was carried out within the period from June 2012 to August 2013.

2.2. Patient selection

Patients were recruited from District TB Centre (DTC) irrespective of their age, sex, religion, socio-economic status or any other demographic profile. All the cases were confirmed as MDR-TB by Culture and Drug Susceptibility Testing (DST) from RNTCP accredited National Reference Laboratory (NRL), New Delhi. After obtaining approval from Institutional Human Ethics Committee, informed consents of patients were taken. Detailed history taking and pre-treatment evaluation as per RNTCP DOTS Plus Guidelines were done, which included weight and height of the patients, Complete Blood Count, Blood sugar, Liver Function Tests, Blood Urea and Serum Creatinine to assess the Kidney function, Urine examination, Pregnancy test for all women in the child bearing age group and Chest X-ray besides the estimations of Thyroid hormones, viz., TSH, Total T3, Total T4, Free T3 and Free T4. Patients having history of any thyroid disease, other co-morbid diseases, pregnant women or patient having h/o radiotherapy were *excluded* from the study. A total of 114 patients were diagnosed as MDR-TB cases and put on DOTS Plus treatment till August 2013. Out of them, 11 patients died, 3 were dropouts and 1 patient was co-infected with HIV making our study group to 99 MDR-TB patients. So, equal number of age- and sex-matched voluntary healthy subjects was taken as controls. 76 MDR-TB patients completed 6 months or more of DOTS Plus treatment till conclusion of our study.

2.3. Measurement of thyroid hormones

Blood samples were collected in vacutainers under all aseptic and antiseptic conditions and serum was separated by centrifugation. Tests for serum Thyroid Stimulating Hormone

(TSH), Total T3, Total T4, Free T3 and Free T4 were performed by chemiluminescence method in Beckman Coulter Access2 Immunoassay System. Serum Hypersensitive TSH done here was a 3rd generation test[7] and all the thyroid hormones were assayed on the same day of sample collection under standard assay protocol using reagents from Beckman Coulter, USA.[8–12] Quality control was maintained by using Bio-Rad internal quality control samples and external quality control by samples from Association of Clinical Biochemists of India (ACBI) prepared by Christian Medical College (CMC), Vellore. During the study period, the %CV of the parameters TSH, Total T3, Total T4, Free T3 and Free T4 were 1.96, 2.03, 3.34, 1.66 and 3.43, respectively.

2.4. *Data collection and analysis*

All the patients were prospectively followed from June 2012 when the first patient was put on DOTS Plus treatment in EKH district of Meghalaya. Out of the 99 cases, 76 have completed 6 months or more of DOTS Plus regimen till August 2013. So, thyroid hormones were again measured in them after 6 months of completion of DOTS Plus. Statistical analysis of the data was performed by using Microsoft Excel software. A '*p*' value of less than or equal to 0.05 was considered significant.

3. Results

In our study, out of the 99 cases, 63 were males and 36 were females. The mean age of study population was 32.29 ± 12.98 years with a range from 11 to 85 years. Age distribution of the study subjects is shown in Fig. 1. Complete Blood Count, Blood sugar and Liver and Kidney Function Test results of all the patients were within normal limits. The mean concentrations of the thyroid hormones for all the 99 cases and controls are represented in Table 1 along with their statistical significance. From the table it is evident that there was no significant difference of thyroid hormone concentrations between Pre-treatment cases and control group. If we see the gender wise distribution of the concentrations of all the thyroid hormones in the 99 cases, then it is seen that in the 63 males the mean concentration of serum TSH was 2.37 ± 1.34 μIU/mL and the same for 36 female cases was 2.92 ± 1.82 μIU/mL. Likewise, the differences between the concentrations for Total T3, Total T4, Free T3 and Free T4 between male and female cases are also statistically not significant. In Table 2, the mean concentrations of the thyroid hormones for all the cases and follow-ups are represented along with their gender wise distribution and statistical significances. From Fig. 2, the differences of thyroid profile between pre-treatment evaluation and at 6 months of DOTS Plus treatment can be easily visualized. All the patients were given the same 6 drugs in their intensive phase as per their body weight. The results for the only patient, who is co-infected with HIV and hence excluded from our analysis, receiving PAS along with these 6 drugs, are shown in Table 3. The elevation in serum TSH concentration after completion of 6 months of intensive therapy can be easily ascertained from Fig. 3.

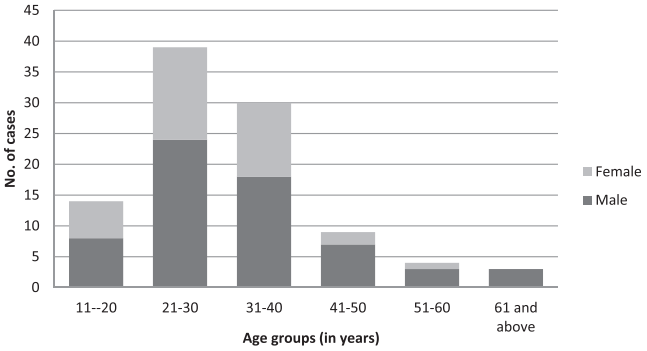


Fig. 1 – Age distribution of cases.

Table 1 – Comparison of thyroid profile of cases before starting treatment and controls.

Variables		Mean ± SD	Reference range[a]	Significance level (*p*)
TSH (μIU/mL)	Cases (Pre-treatment)	2.50 ± 1.37	0.34–5.60	>0.05
	Controls	2.58 ± 1.48		
Total T3 (ng/mL)	Cases (Pre-treatment)	1.22 ± 0.62	0.87–1.78	>0.05
	Controls	1.28 ± 0.57		
Total T4 (μg/dL)	Cases (Pre-treatment)	9.36 ± 2.17	6.09–12.23	>0.05
	Controls	9.32 ± 2.06		
Free T3 (pg/mL)	Cases (Pre-treatment)	3.28 ± 0.48	2.50–3.90	>0.05
	Controls	3.21 ± 0.42		
Free T4 (ng/dL)	Cases (Pre-treatment)	0.87 ± 0.37	0.61–1.12	>0.05
	Controls	0.89 ± 0.39		

[a] From the product inserts for Access TSH, Total T3, Total T4, Free T3 and Free T4 assay by Beckman Coulter, Inc. Brea, CA 92821.

Table 2 – Gender wise distribution of thyroid profile in patient group.

Variables	Male	Mean ± SD	Significance level (p)	Female	Mean ± SD	Significance level (p)
TSH (μIU/mL)	Pre-treatment	2.34 ± 1.25	<0.0001	Pre-treatment	2.78 ± 1.55	<0.0001
	After 6 months	6.50 ± 2.17		After 6 months	7.17 ± 2.65	
Total T3 (ng/mL)	Pre-treatment	1.26 ± 0.73	0.26	Pre-treatment	1.16 ± 0.35	0.21
	After 6 months	1.18 ± 0.31		After 6 months	1.07 ± 0.31	
Total T4 (μg/dL)	Pre-treatment	9.22 ± 2.23	<0.05	Pre-treatment	9.62 ± 2.06	<0.05
	After 6 months	8.64 ± 2.05		After 6 months	8.98 ± 1.68	
Free T3 (pg/mL)	Pre-treatment	3.27 ± 0.48	<0.05	Pre-treatment	3.29 ± 0.49	<0.05
	After 6 months	2.82 ± 0.39		After 6 months	2.61 ± 0.62	
Free T4 (ng/dL)	Pre-treatment	0.82 ± 0.17	<0.001	Pre-treatment	0.95 ± 0.57	<0.001
	After 6 months	0.70 ± 0.13		After 6 months	0.74 ± 0.23	

Pre-treatment group: No. of males = 63, No. of females = 36, Total = 99.
After 6 months: No. of males = 51, No. of females = 25, Total = 76.

4. Discussion

The present study revealed that thyroid hormone levels were altered in MDR-TB patients under DOTS Plus. As per Fig. 1, most of the cases (70%) are occurring within the age group of 20–40 years, i.e., in the most active period of the lives of the individuals. Although India is among those countries where iodine intake tends to be adequate,[13] to avoid any discrepancy, the pre-treatment thyroid profile of the patients was compared with equal number of age- and sex-matched controls with same dietary habits, which revealed that there was no significant difference with the baseline thyroid profile of the general population (Table 1). If we see gender wise, then increase in serum TSH concentration is statistically very significant. As per Table 2, decreases in Serum Total T4, Free T3 and Free T4 levels are also significant. Although there is slight decrease in mean serum Total T3 levels after 6 months of intensive therapy, they are statistically not significant as $p > 0.05$. A significant increase in serum TSH concentration has been noted in patients after 6 months of treatment, which is evident from Fig. 2 and statistically very significant too. Out of the 76 patients screened for thyroid profile after 6 months of treatment, 52 (68%) are showing TSH levels more than the reference limit of 5.60 μIU/mL and 5 patients (7%) have TSH value more than 10 μIU/mL. But none of them complained of any specific symptoms of hypothyroidism nor is any clinically evident thyroid swelling present till now, which suggests presence of sub-clinical hypothyroidism, although they presented with generalized ill health and were admitted to DTC. If we refer to similar studies by Chhabra et al., they have found clinically evident hypothyroidism in 11% of cases.[14] In another study by Satti et al., occurrence of hypothyroidism was 69% where they have defined hypothyroidism as at least one TSH value >10.0 μIU/mL.[15] In a prospective study carried out by Modongo and Zetola in Botswana, evidence of hypothyroidism was found to be 34.3%.[16] The exact cause of hypothyroidism is still unclear but the most offending agents are Ethionamide and PAS.[17] Drucker et al. studied the goitrogenic effect in vitro by incubating ethionamide in various concentrations (10^{-3} to 10^{-7} mol/L) with ovine thyroid cells in tissue cultures. Ethionamide inhibited the trapping of technetium and organification of iodine at concentrations seen clinically (10^{-5} mol/L). Hence, ethionamide appeared to be a potential goitrogen in susceptible persons.[18] PAS is also having inhibitory effect on thyroid gland. The synergistic inhibitory effect of these two drugs on thyroid gland can be seen on the

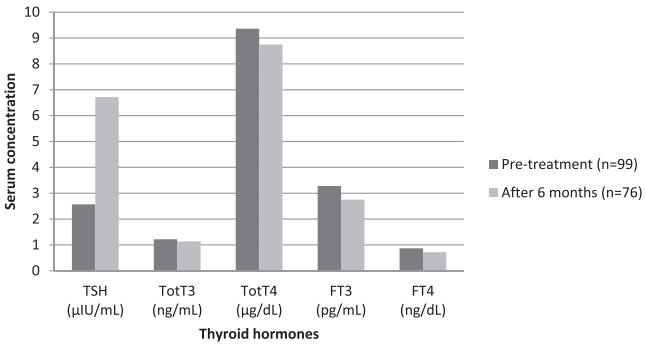


Fig. 2 – Comparison of thyroid profile in patient group.

Table 3 – Comparison of thyroid profile in the patient getting ethionamide-PAS combination.

Variables		Serum concentration	Reference range[a]
TSH (μIU/mL)	Pre-treatment	3.94	0.34–5.60
	After 6 months	30.71	
Total T3 (ng/mL)	Pre-treatment	1.16	0.87–1.78
	After 6 months	1.30	
Total T4 (μg/dL)	Pre-treatment	11.00	6.09–12.23
	After 6 months	9.12	
Free T3 (pg/mL)	Pre-treatment	3.36	2.50–3.90
	After 6 months	3.19	
Free T4 (ng/dL)	Pre-treatment	0.94	0.61–1.12
	After 6 months	0.63	

[a]From the product inserts for Access TSH, Total T3, Total T4, Free T3 and Free T4 assay by Beckman Coulter, Inc. Brea, CA 92821.

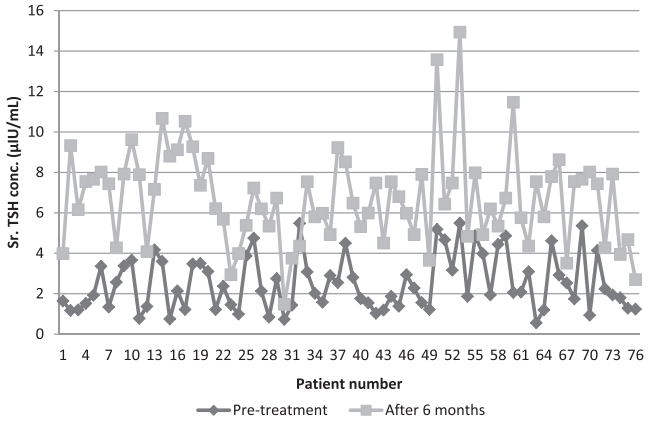


Fig. 3 – Comparison of TSH concentrations in study subjects.

TSH level of the only patient who is getting a combination of both the drugs in our study, as his serum TSH levels are increased by almost 10 times after 6 months of DOTS Plus treatment. But other factors cannot be ruled out as the patient is getting anti-retroviral therapy also.

5. Conclusion

MDR-TB is mostly a man-made phenomenon as poor treatment, poor drugs and poor adherence lead to the development of MDR-TB. Although any conclusion based on available evidence is preliminary, the frequency of drug-induced hypothyroidism in patients exposed to MDR-TB is increasing. Hence, early screening and intervention, if required for all patients taking DOTS Plus, should be done. Specific protocols are to be formulated under our National Programme for mandatory monitoring of thyroid profile at least every 6 months if not earlier when patient is under DOTS Plus regimen instead of waiting for clinical indications, so that development of hypothyroidism can be detected at the earliest and treatment default can be minimized.

Sources of support: Existing facility at Dept. of Biochemistry, NEIGRIHMS.

Conflict of interest

The authors have none to declare.

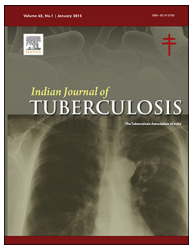
REFERENCES

1. Chakraborty AK. Epidemiology of tuberculosis: current status in India. *Indian J Med Res*. 2004;120:248–276.
2. TB India 2013. *RNTCP- Annual Status Report; Directorate General of Health Services*. New Delhi: Ministry of Health & Family Welfare; 2013:34–37.
3. As per data received from District TB Office, East Khasi Hills District, Shillong, Meghalaya, India 793002.
4. World Health Organization (WHO) Global Tuberculosis Report 2013. (WHO/HTM/TB/2013.11). Geneva; 2012. p. 47.
5. Towards universal access to diagnosis and treatment of multidrug-resistant and extensively drug-resistant tuberculosis by 2015: WHO Progress Report 2011. p. 4.
6. RNTCP Response to Challenges of Drug resistant TB in India, Directorate General of Health Services, Ministry of Health & Family Welfare, New Delhi; January 2012 (Update).
7. Alexander Jr. RL. The diagnostic importance of third-generation methods for the assay of thyrotropin (TSH). American Clinical Laboratory, 18, December 1994 - January 1995.
8. Beckman Coulter, Inc. Access HYPERsensitive hTSH product insert, Brea, CA 92821.
9. Beckman Coulter, Inc. Access Total T3 product insert, Brea, CA 92821.
10. Beckman Coulter, Inc. Access Total T4 product insert, Brea, CA 92821.
11. Beckman Coulter, Inc. Access Free T3 product insert, Brea, CA 92821.
12. Beckman Coulter, Inc. Access FreeT4 product insert, Brea, CA 92821.
13. De Benoist B, Andersson M, Egli I, Takkouche B, Allen H. *Iodine status worldwide. WHO Global Database on Iodine Deficiency*. Geneva: World Health Organization (WHO); 200428.
14. Chhabra N, Gupta N, Aseri ML, Mathur SK, Dixit R. Analysis of thyroid function tests in patients of multidrug resistance tuberculosis undergoing treatment. *J Pharmacol Pharmacother*. 2011;2(4):282–285.
15. Satti H, Mafukidze A, Jooste PL, McLaughlin MM, Farmer PE, Seung KJ. High rate of hypothyroidism among patients treated for multidrug-resistant tuberculosis in Lesotho. *Int J Tuberc Lung Dis*. 2012;16(4):468–472.
16. Modongo C, Zetola NM. Prevalence of hypothyroidism among MDR-TB patients in Botswana. *Int J Tuberc Lung Dis*. 2012;16(11):1561–1562.
17. Revised National Tuberculosis Control Programme: Guidelines on Programmatic Management of Drug Resistant TB (PMDT) in India, Central TB Division, Directorate General of Health Services, Ministry of Health & Family Welfare, Nirman Bhavan, New Delhi; May 2012, p. 81.
18. Drucker D, Eggo MC, Salit IE, Burrow GN. Ethionamide induced goitrous hypothyroidism. *Ann Intern Med*. 1984;100:837–839.

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: http://www.journals.elsevier.com/indian-journal-of-tuberculosis/



Original Article

Alcohol use disorders among pulmonary tuberculosis patients under RNTCP in urban Pondicherry, India

A.M. Veerakumar [a,*], Swaroop Kumar Sahu [a], Sonali Sarkar [a], Shivanand Kattimani [b], S. Govindarajan [c]

[a] Department of Preventive and Social Medicine (P&SM), Jawaharlal Institute of Postgraduate Medical Education and Research (JIPMER), Puducherry 605006, India
[b] Department of Psychiatry, Jawaharlal Institute of Postgraduate Medical Education and Research (JIPMER), Puducherry 605006, India
[c] State Tuberculosis Officer, Puducherry, India

ARTICLE INFO

Article history:
Received 14 July 2015
Accepted 20 July 2015
Available online 9 October 2015

Keywords:
Alcohol use disorder
AUDIT
Pulmonary tuberculosis
Urban
Pondicherry

ABSTRACT

Background: Alcohol use is implicated in a wide variety of diseases and disorders including TB.
Objectives: To study the prevalence and pattern of alcohol use among the PTB patients registered under RNTCP in urban Pondicherry and the association of various socio-demographic variables with alcohol drinking during treatment.
Methods: A cross-sectional study was conducted among 235 PTB patients from 6 randomly selected urban PHCs of Pondicherry from Jan 2013 to March 2014. Alcohol Use Disorder Identification Test (AUDIT) was used for screening the PTB patients for their severity of alcohol use. Data were entered in Epi-data v3.1 and was analyzed by SPSS v20. Chi-square test and multiple-logistic regression were used.
Results: Prevalence of alcohol use among PTB patients at the time of diagnosis was 59% and during treatment was 31.5%. Around 54% PTB patients had alcohol use disorders (AUD) during diagnosis, whereas the same during treatment was 26.4%. Among drinkers at the time of diagnosis ($n = 139$), 80% modified and 20% did not modify their alcohol use even after TB diagnosis. Male gender was significantly associated with alcohol use ($p \leq 0.001$). Univariate analysis showed that lower level of education, lower SES, unemployed/unskilled/semiskilled/skilled occupational group, and Category II were significantly associated with alcohol use among male patients ($p < 0.05$). Multivariate analysis showed that none of the variables were associated.
Conclusions: One-third of PTB patients were drinking alcohol during the treatment. Though 80% modified alcohol use after TB diagnosis, the rest 20% did not modify. Necessary interventions need to be planned to screen for alcohol use.

* *Corresponding author at*: Department of Preventive and Social Medicine, 4th floor, Administrative Block, JIPMER, Dhanvantari Nagar, Puducherry 605006, India. Tel.: +91 04132296391/8124734933; fax: +91 04132272066.
E-mail address: dr.veera10@gmail.com (A.M. Veerakumar).

http://dx.doi.org/10.1016/j.ijtb.2015.07.017

1. Introduction

Tuberculosis continues to be a major public health problem in the world.[1] India is one of the high TB burden countries contributing to almost 1/4th of global TB cases. As per WHO estimated burden of tuberculosis in India in 2012, the incidence of TB was 176 per 100,000 and the prevalence was 230 per 100,000 population.[1]

Alcohol use is implicated in a wide variety of diseases, disorders and injuries, including TB.[2] The association of alcohol use and tuberculosis had been known for a long time, even before the aetiology of tuberculosis was known. Benjamin Rush as early as 1785 listed tuberculosis and pneumonia as infectious squeal of sustained heavy alcohol use.[3] Alcohol use significantly increases the risk of active TB.[2] This may be due to increased risk of infection related to specific social mixing patterns associated with alcohol use and also as a result of decreased immunity among the alcohol users. Jurgen Rehm et al.[4] found that heavy alcohol use strongly predicts both the incidence and adverse outcome of tuberculosis. Heavy alcohol use was found to be linked to altered pharmacokinetics of TB medication, social marginalization and drift, higher re-infection rate, higher default rate and development of multi-drug resistant TB. It has also been found that there is delay in diagnosis of TB among the TB suspects with the history of alcohol abuse.[5] In India, alcohol intake is one of the major risk factors for treatment non-compliance and mortality under DOTS (directly observed treatment, short-course) therapy.[6] Even though the ill effects of alcohol use are well known, health care providers in India do not routinely screen for 'alcohol use disorders' (AUD) while treating for TB. Screening for AUD among TB patients is routinely carried out in developed countries like Russia.[7]

Screening for alcohol disorders is expected to improve TB treatment outcomes by planning appropriate intervention. In the present study, Alcohol Use Disorders Identification Test (AUDIT) was used to screen the PTB patients for assessing their magnitude of alcohol use. The objectives were to study the prevalence and pattern of alcohol use among the pulmonary tuberculosis patients registered under RNTCP in urban Pondicherry and to study the association of various socio-demographic variables with alcohol drinking during treatment.

2. Materials and methods

This was a community-based cross-sectional study carried out between January 2013 and March 2014 in Pondicherry district. The total population of Pondicherry[8] is 12,44,464. Around 68% of populations in Pondicherry live in urban areas.

The sample size was calculated to be 235 by using the prevalence of alcohol use among tuberculosis patients, aged 15 years and above, and was 29% in urban area,[9] with relative precision of 20% and 95% confidence interval. The study was restricted to urban PHCs of Pondicherry. Six out of 12 urban PHCs[10] were selected randomly till the cumulative total of PTB patients of previous year satisfied the sample size necessary for the study. Inclusion criteria were PTB patients aged 15 years and above. Category IV tuberculosis patients were excluded. All the eligible consecutive PTB patients from selected six PHCs were included in the study. The location of these PHCs was scattered all over urban Pondicherry, thus this was expected to represent total PTB patients of urban Pondicherry. Eligible patients were interviewed in the Continuation Phase (CP) of their TB treatment. During the Intensive Phase (IP) of TB treatment, patients are frequently monitored by health worker. Thus during the IP, patient motivation to follow advice and adopt healthy lifestyle is high, study during the IP may falsely undermine the magnitude of alcohol use. Interviewing them during the CP of TB treatment may reflect the true picture of alcohol use pattern.

The study was approved by the Institute Ethics Committee. Demography details of eligible PTB patients were obtained from the TB treatment cards maintained for each patient in their respective PHCs. All the eligible TB patients were contacted at their place of residence. Adequate time was spent with each PTB patient to build up rapport with them, and informed consent was taken from participants before collecting information. The houses which were either locked or where the patient was not present at the time of the visit were revisited one more time at a later date. Patient who could not be contacted during the 2nd visit was not contacted further.

2.1. Study tools

A pre-tested interview schedule was used to collect information from the study participants' socio-demographic factors such as age, gender, education and occupation were obtained from the subject by personal interview. Education status was classified based on the Tamil Nadu Education Board.[11] Socio-economic status was classified using Modified Kuppusamy classification – 2012[12] for the urban areas. Occupation was classified using National Classification of Occupations, 2004.[13]

The Alcohol Use Disorder Identification Test (AUDIT)[14] was used to assess TB patients alcohol use status, and accordingly, alcohol dependence level was categorized as low risk, hazardous or harmful use and probable alcohol dependence. AUDIT has 10 items. Each of the items had a score ranging from 0 to 4; thus, the total score was 40. Aggregate score of less than 8 was interpreted as Low risk and score of 8 or more was considered to have Alcohol Use Disorder (AUD). AUD meant that the person's pattern of alcohol use was hazardous or harmful to his health (Score 8–19), or person probably suffers from alcohol dependence (Score ≥ 20).

2.2. Definitions

Ever Drinker: those who had consumed alcohol anytime in the past; *Current Drinker:* those who had consumed alcohol in the past one year; *Former Drinker:* those who had consumed alcohol before the past one year; *Never Drinker (Lifetime abstainers)*: those who had not consumed alcohol anytime in the past. In our study, following operational definitions were used. *Drinkers at the time of diagnosis:* PTB patients who consumed alcohol anytime during the period, one year before the date of interview to till the time of diagnosis; *Drinkers during treatment*: PTB patients who consumed alcohol any time after the diagnosis to till the date of interview.

The PTB patients were interviewed to assess the status of their alcohol use both before and after TB diagnosis by using the same set of questions as given in the AUDIT questionnaire. The status of alcohol intake at the time of diagnosis and during treatment was captured. Subjects were asked regarding their perceived behaviour change such as discontinued/reduced/maintained the same level/increased alcohol use after their TB diagnosis as compared to their status of alcohol use before TB diagnosis.

2.3. *Data analysis*

Data were collected and entered in the Epidata version 3.1.[15] It was exported to excel and was analyzed using IBM SPSS version 20.[16] Description of all socio-demographic variables and alcohol prevalence among PTB patients was reported in percentages. Pattern of alcohol use and its severity was also reported in percentages. Association between socio-demographic variables and alcohol use was analyzed by using the Chi-square test. Multiple logistic regression was used to find out the independent variable for alcohol use among PTB patients. Adjusted odds ratio was given.

3. Results

Out of the total 265 pulmonary tuberculosis patients registered in the select 6 PHCs during the study period, 235 (88.7%) were included and 30 (11.3%) patients could not be contacted in the study. Among the 30 PTB patients, 11 (4.6%) could not be contacted even after two house visits (not available in both occasions); 15 (5.6%) had shifted the residence, which was recorded as ''change of address'' in RNTCP treatment card and 4 (1.5%) had died while on treatment. The mean (SD) time interval between initiation of CP of TB treatment and data collection was 12 ± 4 weeks.

3.1. *Socio-demographic details*

Majority of the PTB patients were males (79.6%). Mean (SD) age was 44 ± 14 years. Majority (44%) of the PTB patients were educated up to Upper primary/Secondary class (Class 6–10), 28.5% had No formal education/Primary class (Class 1 to 5) and another 27.5% had education beyond Class 10 (Higher secondary/Graduate). Nearly 70% of them were working in Unskilled/Semiskilled/Skilled jobs, 13% were Unemployed and the rest 17% were working as Professionals/Businessmen. Nearly half (49%) of them belonged to lower SES. More than three-fourth of PTB patients received Cat I (77%) treatment and the rest were put on Cat II regimen (Table 1).

Table 1 – Socio-demographic details of PTB patients from urban PHCs of Pondicherry (2013–2014).

Variables	N (%)
Age group	
15–29	41 (17.5)
30–44	81 (34.5)
45–59	80 (34.0)
≥60	33 (14.0)
Gender	
Male	187 (79.6)
Female	48 (20.4)
Education status	
No formal education/Primary class	67 (28.5)
Upper primary/Secondary class	103 (43.8)
Higher secondary/Graduate	65 (27.7)
Occupation	
Unemployed	32 (13.6)
Unskilled/Semiskilled/Skilled	163 (69.4)
Professional/Businessman	40 (17.0)
Socio-Economic class	
Upper and middle class	120 (51.1)
Lower class	115 (48.9)
Category of TB treatment	
Cat I	181 (77)
Cat II	54 (23)
Total	235 (100)

3.2. *Alcohol use status*

Out of 235 PTB patients, 148 (63%) patients were *Ever Drinkers*. A total of 9 patients stopped alcohol one year prior to the interview and rest 139 were drinkers at the time of diagnosis. Prevalence of *Drinkers at the time of diagnosis* was 59% (Fig. 1). At the time of diagnosis, PTB patients at Low risk were 5.5% and patients with AUD were 53.6%. Harmful or Hazardous drinkers and Probable alcohol dependence were 39.7% and 15.7%, respectively.

Among the 139 drinkers at the time of diagnosis, 111 (79.8%) patients modified their alcohol usage after being diagnosed with TB and the rest 28 (20.1%) patients continued to drink without modifying their drinking behaviour. Among the 111 patients who modified their alcohol usage after TB diagnosis, 65 patients (58.6%) discontinued and 46 (41.4%) reduced their alcohol use. There were altogether 74 patients who drank alcohol during their treatment. Prevalence of *drinkers during treatment* was 31.5% ($n = 74$).

During CP of treatment, PTB patients at Low risk were 5.1% and AUDs were 26.4%. Harmful or Hazardous drinkers and Probable alcohol dependence were 23.8% and 2.5%, respectively.

3.3. *Association between alcohol use and socio-demographic variables*

The prevalence of alcohol use during treatment among the male PTB patients was 39% whereas the same among the females was 2.1% (Table 2). Alcohol use was significantly associated with male PTB patients ($p \leq 0.001$). There was only one female PTB patient who was taking alcohol. Including the lone female PTB patient in the analysis will falsely undermine the prevalence of alcohol use. Taking this in to consideration, further analysis was restricted to male PTB patients.

There was no difference among the age groups with *drinkers during treatment* ($p = 0.22$) (Table 3). Lower educational groups like No formal education/Primary class and Upper primary/Secondary class were in higher proportion with alcohol use compared to education beyond class 10, and this was found to be significant ($p = 0.009$). Similarly, lower occupational group like Unemployed and Unskilled/Semiskilled/Skilled group had significantly higher proportion with *drinkers during treatment* compared to Professionals/Businessman ($p = 0.009$). Lower SES

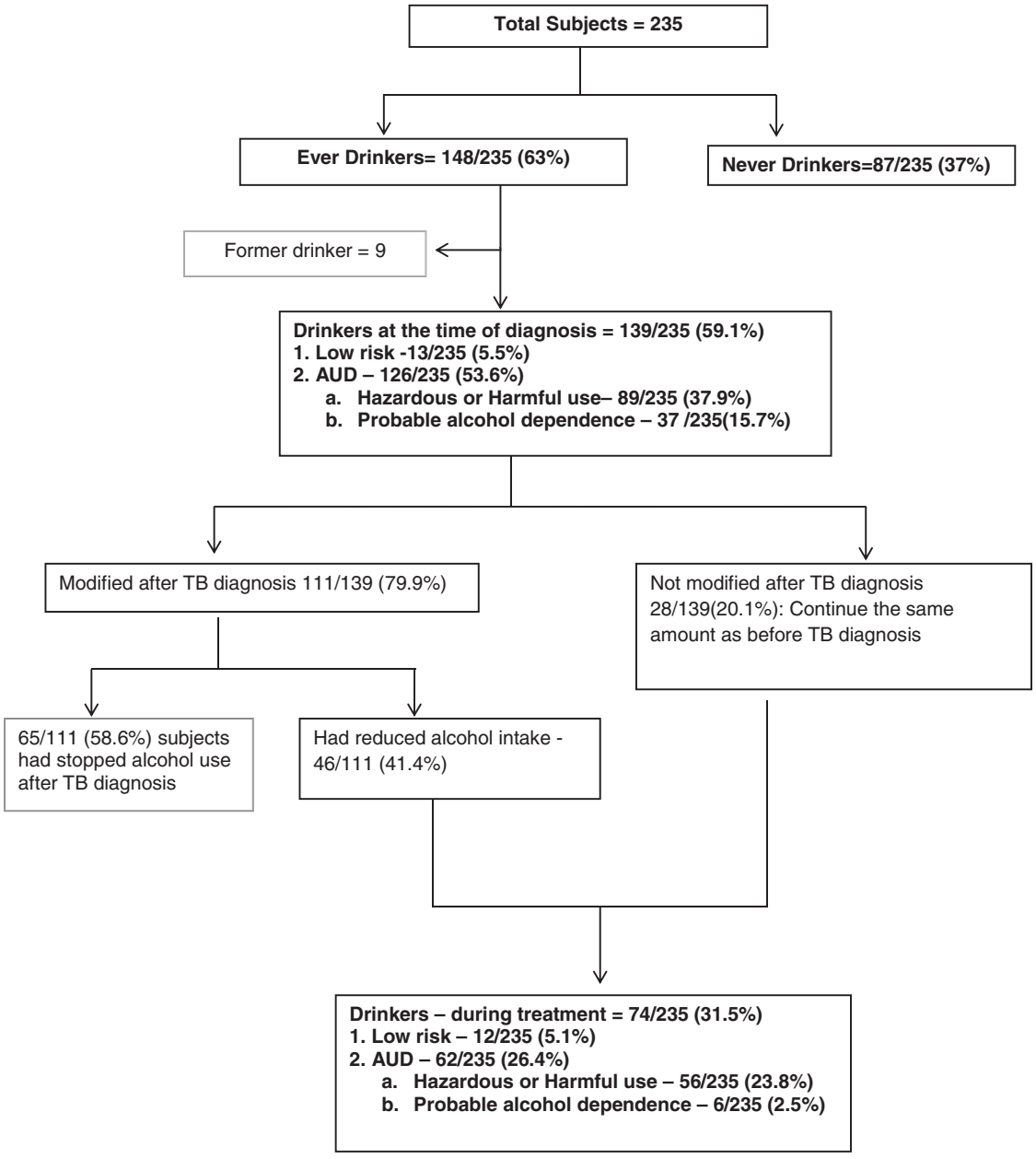


Fig. 1 – Alcohol use among PTB patients in urban PHCs of Pondicherry.

class male PTB patients who were taking alcohol during the treatment were statistically more as compared to patients belonging to middle/upper class ($p = 0.03$). Similarly, Cat II male PTB patients taking alcohol during the treatment were statistically more as compared to Cat I patients ($p = 0.04$). Though univariate analysis showed that there was association between alcohol use with lower education, Unemployed and Unskilled/Semiskilled/Skilled occupation group, lower SES, Cat II treatment, but Multivariate logistic regression by using enter method showed none of the these variables

Table 2 – Association of gender with *drinkers during treatment* among the urban PTB patients of Pondicherry.

Gender	Drinker (%)	Non-drinker (%)	Total (%)	χ^2 (df)	p value
Male	73 (39.0)	114 (61.0)	187 (100)	24.178 (1)	<0.001*
Female	1 (2.1)	47 (97.9)	48 (100)		
Total	74 (31.5)	161 (68.5)	235 (100)		

χ^2 – Chi-square test; df – degrees of freedom.
* p value significant.

Table 3 – Association between socio-demographic variables and *drinkers during treatment* among male PTB patients from urban Pondicherry.

Variables	Drinker (%) N = 73	Non-drinker (%) N = 114	Total (%) N = 187	χ^2 (df)	*p* value
Age group in years					
15–29	3 (18.8)	13 (81.2)	16 (100)	4.43 (1)	0.22
30–44	32 (43.8)	41 (56.2)	73 (100)		
45–59	30 (41.7)	42 (58.3)	72 (100)		
≥60	8 (30.8)	18 (69.2)	26 (100)		
Educational status					
No formal education/Primary class	26 (48.1)	28 (51.9)	54 (100)	9.4 (2)	0.009*
Upper primary/Secondary class	38 (43.2)	50 (56.8)	88 (100)		
Higher secondary/Graduate	9 (20.0)	36 (80.0)	45 (100)		
Occupational status					
Unemployed	8 (32.0)	17 (68.0)	25 (100)	9.32 (2)	0.009*
Unskilled/Semiskilled/Skilled	61 (45.2)	74 (54.8)	135 (100)		
Professional/Businessman	4 (14.8)	23 (85.2)	27 (100)		
Socio-economic status					
Upper and Middle class	27 (28.1)	69 (71.9)	96 (100)	9.87 (1)	0.002*
Lower class	46 (50.5)	45 (49.5)	91 (100)		
PTB category					
Cat I	47 (34.6)	89 (65.4)	136 (100)	4.2 (1)	0.04*
Cat II	26 (51.0)	25 (49.0)	51 (100)		

χ^2 – Chi-square test; df – degrees of freedom.
* *p* value significant.

associated with alcohol use during treatment among male PTB patients (Table 4).

3.4. *Pattern of alcohol use*

Most of the male PTB patients were taking alcohol in form of arrack (49.3%) and Brandy (30.1%). Around 37% of the male PTB patients were taking alcohol 2 to 4 times a month followed by monthly or less (30%). Around 70% of male PTB patients were taking 5 to 6 drinks of alcohol on a typical day (Table 5).

3.5. *Treatment outcome*

Among the total PTB patients, cured rate, completed rate, default rate, failure rate and mortality rate were 73.2%, 12.3%, 6.8%, 5.1% and 2.6%, respectively. There were no differences between alcohol users during TB treatment and non-alcohol users (Table 6).

Table 4 – Logistic regression of socio-demographic variables with *drinkers during treatment*.

Variables	Adjusted odds ratio (CI)	*p* value
Educational status		
No formal education/Primary class	2.2 (0.6–7.8)	0.24
Upper primary/Secondary class	1.6 (0.5–4.9)	0.41
Higher secondary/Graduate	1	
Occupational status		
Unemployed	1.1 (0.2–5.7)	0.91
Unskilled/semiskilled/skilled	2.3 (0.6–9.2)	0.22
Professional/Businessman/Student	1	
SES		
Upper and Middle class	1	
Lower class	1.6 (0.7–3.4)	0.22
Category of TB treatment		
Cat I	1	
Cat II	1.8 (0.9–3.4)	0.11

4. Discussion

In the present study, prevalence of alcohol use among the PTB patients at the time of TB diagnosis was 59%, whereas the same during CP of treatment was 31.5%. There was decrease in

Table 5 – Type of alcohol, frequency and quantity of alcohol intake among the male alcohol drinkers during treatment from the urban PHCs of Pondicherry.

Variables	N (%)
Type of alcohol use	
Arrack	36 (49.3)
Brandy	22 (30.1)
Beer	11 (15.1)
Whisky	4 (5.5)
Frequency	
Monthly or less	22 (30.1)
2 to 4 times a month	27 (37.0)
2 to 3 times a week	12 (16.4)
4 or more times a week	12 (16.4)
No of drinks*	
1 to 2	3 (4.1)
3 to 4	14 (19.2)
5 to 6	52 (69.9)
7 to 9	5 (6.8)
Total	73 (100)

* One drink = 30 ml of hard liquor = 45 ml of wine = 33 ml of arrack (1/3 packet) = ½ bottle (650 ml) of strong beer = 650 ml of regular beer.

Table 6 – Treatment outcome among alcohol users in urban PTB patients of Pondicherry.

Treatment outcome	Drinker N (%)	Non-drinker N (%)	Total N (%)	χ^2 value (df)	p value
Cured/Completed	61 (82.4)	140 (87.0)	201 (85.5)	0.84 (1)	0.36
Default/Failure/Died	13 (17.6)	21 (13.0)	34 (14.5)		
Total	74 (100)	161 (100)	235 (100)		

χ^2 – Chi-square test; df – degrees of freedom.

the proportion of AUDs from 53.6% during diagnosis to 26.4% during treatment. This decrease could be because of the counselling sessions inbuilt in delivery of RNTCP services. There were 28 patients who had continued taking alcohol without modifying their behaviour even after TB diagnosis. These patients are of concern for effective implementation of RNTCP, as achieving favourable outcome becomes difficult. Moreover, there were 6 (2.5%) PTB patients, who were probably alcohol dependent during treatment. These patients need to be referred to the specialist de-addiction services for further management.

A study done in Chennai by Suhadev et al.[9] found that the prevalence of alcohol use among TB patients was 29%, and alcohol use disorder was found to be 52% among the drinkers. In the present study, around 31.5% of PTB patients were taking alcohol during treatment and 84% had AUD among the drinkers during treatment. This difference in the findings of present study, as compared to Chennai study, could be due to difference in the time of interview from TB diagnosis. The present study interviewed the patients during the CP of TB treatment. This was not clear in the Chennai study (interviewed during diagnosis/treatment).

Another study done in South Africa, using AUDIT questionnaire among TB patients by Karl Peltzer et al.[17] in 42 Primary care clinics, found that the overall AUD were 23%, which is comparable with our study where AUDs were found to be 26.4% among the total TB patients.

In the present study, prevalence of alcohol use among the PTB patients at the time of diagnosis was 59.1%. A study by Kolappan et al.[5] from Chennai found that the prevalence of alcohol use at the time of diagnosis was 32.4% among the PTB patients. Vikas G. Rao et al.[18] from Madhya Pradesh have found that the prevalence of alcohol use was 20% among the PTB patients at the time of diagnosis.

In our study, prevalence of alcohol use among male PTB patients was 39%. There was only one female patient taking alcohol during treatment. A study done in Chennai by Suhadev et al.[9] found that there were no drinkers among the females. However, the study done in South Africa by Karl Peltzer et al.[17] found that 13% of the females were having AUDs. The difference between the present study and the study in South Africa could be due to the difference in socio-cultural factors between the two countries.

In the present study, there was no association between age group and alcohol use. By univariate analysis, it was found that lower level education, unemployed/unskilled/semiskilled/skilled occupation, lower SES and Cat II were significantly associated with alcohol use. Multivariate analysis showed that none of variables were significant.

4.1. *Strengths*

Almost 89% of the PTB patients in the selected 6 PHCs were covered in this study. The location of the 6 selected PHCs were scattered all over urban Pondicherry. It is expected that selected PHCs will be representative of the total urban PTB patients of Pondicherry. Thus, generalization of the study findings can be done to all TB patients in urban Pondicherry. This was one of the few studies, which assessed the prevalence of alcohol use and their severity among PTB patients both at the time of diagnosis and during the CP of TB treatment. It was possible to quantify the change in drinking pattern of PTB patients during diagnosis and during treatment.

4.2. *Limitations*

The present study participants were PTB patients attending government health facilities. Thus, the findings from the study are applicable to PTB patients attending government health facilities only. Another limitation was the likely bias due to self-report on alcohol use by the study participants cannot be ruled out.

5. Conclusion

This study found that 59% PTB patients were alcohol *drinkers at the time of diagnosis* and 31.5% were alcohol *drinkers during the CP of treatment*. Among the drinkers at the time of diagnosis, 80% modified their alcohol intake either by decreasing or discontinuing alcohol after being diagnosed with TB. Health programme needs to concentrate on the rest 20% of PTB patients who continued to take alcohol during treatment; necessary interventions need to be planned for these patients. Health workers need to be trained to screen for AUD at the field for identifying and facilitating appropriate interventions. These interventions are expected to improve the treatment compliance and outcome of TB.

Conflicts of interest

The authors have none to declare.

Acknowledgement

We acknowledge the DOTS providers in the selected PHC's for their help in data collection. We would like to acknowledge the RNTCP OR Committee, Puducherry for providing funding.

REFERENCES

1. TB India 2014. *Revised National Tuberculosis Control Programme Annual Status Report [Internet]*. New Delhi: Central TB Division, Directorate General of Health Services, Ministry of Health and Family Welfare; 2014. Available from: http://www.tbcindia.nic.in/pdfs/TB%20INDIA%202014.pdf Cited 18.8.2014.
2. Lönnroth K, Williams BG, Stadlin S, Jaramillo E, Dye C. Alcohol use as a risk factor for tuberculosis – a systematic review. *BMC Public Health*. 2008;8:289.
3. Rush B. *An Inquiry into the Effects of Ardent Spirits upon the Human Body and Mind: With an Account of the Means of Preventing and of the Remedies for Curing Them*. 8th ed. Exeter, N.H.: Richardson; 1785.
4. Rehm J, Samokhvalov AV, Neuman MG, et al. The association between alcohol use, alcohol use disorders and tuberculosis (TB). A systematic review. *BMC Public Health*. 2009;9:450.
5. Kolappan C, Gopi PG, Subramani R, Narayanan PR. Selected biological and behavioural risk factors associated with pulmonary tuberculosis. *Int J Tuberc Lung Dis Off J Int Union Tuberc Lung Dis*. 2007;11(September (9)):999–1003.
6. Santha T, Garg R, Frieden TR, et al. Risk factors associated with default, failure and death among tuberculosis patients treated in a DOTS programme in Tiruvallur District, South India, 2000. *Int J Tuberc Lung Dis Off J Int Union Tuberc Lung Dis*. 2002;6(September (9)):780–788.
7. Mathew TA, Yanov SA, Mazitov R, et al. Integration of alcohol use disorders identification and management in the tuberculosis programme in Tomsk Oblast, Russia. *Eur J Public Health*. 2009;19(January (1)):16–18.
8. Census of India 2011. *Provisional Population Totals, Puducherry UT [Internet]*. Office of the Registrar General and Census Commissioner, GOI; 2011. Available from: http://www.censusindia.gov.in/2011-prov-results/prov_data_products_puducherry.html Cited 12.8.2014.
9. Suhadev M, Thomas BE, Raja Sakthivel M, et al. Alcohol use disorders (AUD) among tuberculosis patients: a study from Chennai, South India. *PLoS ONE*. 2011;6(5):e19485.
10. Directorate of Health & Family Welfare Services, Government of Puducherry, India [Internet]. Available from: http://www.health.puducherry.gov.in Cited 12.6.2014.
11. Education System in Tamil Nadu [Internet]. Department of School Education, Government of Tamil Nadu. Available from: http://www.tn.gov.in/schooleducation/statistics/picture1-edn.htm Cited 20.7.2014
12. Kumar N, Kishore J, Gupta N. Kuppuswamy's socioeconomic scale: updating income ranges for the year 2012. *Indian J Public Health*. 2012;56(1):103.
13. *National Classification of Occupation*. Minister of Labour: India; 2004.
14. Babor T, Higgins-Biddle J, Saunders J, Monteiro M. *The Alcohol Use Disorders Identification Test: Guideline for use in Primary Care*. Geneva: World Health Organization; 2001.
15. Epidata entry [Internet]. Epidata Association. Available from: http://www.epidata.dk/.
16. IBM SPSS Statistics for Windows. Armonk, NY: IBM Corp; 2013.
17. Peltzer K, Louw J, McHunu G, Naidoo P, Matseke G, Tutshana B. Hazardous harmful alcohol use and associated factors in tuberculosis public primary care patients in South Africa. *Int J Environ Res Public Health*. 2012;9(September (9)):3245–3257.
18. Rao VG, Gopi PG, Bhat J, Yadav R, Selvakumar N, Wares DF. Selected risk factors associated with pulmonary tuberculosis among Saharia tribe of Madhya Pradesh, central India. *Eur J Public Health*. 2012;22(April (2)):271–273.

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: http://www.journals.elsevier.com/indian-journal-of-tuberculosis/

Case Report

Tuberculosis presenting as a sclerosis of bone: A case report

Balbir Malhotra [a], *C.L. Nagaraja* [b,*], *Rahul Prabhu D'sa* [b]

[a] *Associate Professor, GMC, Amritsar, India*
[b] *Junior Resident, GMC, Amritsar, India*

ARTICLE INFO

Article history:
Received 2 June 2014
Accepted 8 July 2015
Available online 6 October 2015

Keywords:
Skeletal tuberculosis
Sclerosis of bone
Differential diagnosis
Clavicle

ABSTRACT

An unusual case of skeletal tuberculosis, presenting as a hard swelling and sclerotic lesion in the medial end of the clavicle is presented. With re-emergence of tuberculosis as an important infection worldwide, and the ability of this disease to mimic many skeletal pathologies, this has to be included in the differential diagnosis, especially at unusual sites.

1. Introduction

Isolated tuberculosis (TB) of the clavicle with absence of involvement of neighboring joint is rare.[1] With re-emergence of TB as an important infection worldwide, more and more cases are being reported with unusual features. Due to its peculiar blood supply, extra-pulmonary TB in the sternoclavicular region is quite uncommon.[10] The clavicle is an uncommon site of skeletal tuberculosis, reportedly accounting for less than one percent of cases,[2] and the presentation at this site may frequently be atypical, leading to diagnostic confusion, and to delays in appropriate therapy. In the few reports available, the lateral end of the clavicle has been found to be less frequently diseased than the medial end.[2–4] Moreover, tuberculosis has been known to mimic all types of lesions; in the absence of pulmonary lesions and other concomitant features, atypical radiographic picture may not bring the diagnosis primarily to mind.[5]

2. Clinical record

A 35-year-old female presented to us with hard swelling lesion in right parasternal in the upper part of 3–4 months. The lesion was gradually progressive in nature. For this complaint, she visited many physicians and was prescribed various antibiotics but there was no relief of pain. There was no history of trauma, cough, pain chest, dyspnea, or fever. Past history was insignificant. There was no history of tuberculosis and no one in the family had a history of tuberculosis.

Clinical examination revealed a hard swelling lesion of 2 cm × 2.5 cm × 1 cm in the medial end of right clavicle. There was no evidence of cervical or axillary lymphadenopathy and the lung fields were essentially clear. Routine investigations of complete blood count were within normal limits. Renal and hepatic panels were within normal limit. ESR was 35 mm and tuberculin skin test is positive. HIV-I and II were negative. Chest X-ray was grossly normal (Fig. 1) except sclerosis of the

* *Corresponding author*. Tel.: +91 0977937563.
E-mail address: naraju.doc@gmail.com (C.L. Nagaraja).
http://dx.doi.org/10.1016/j.ijtb.2015.09.007

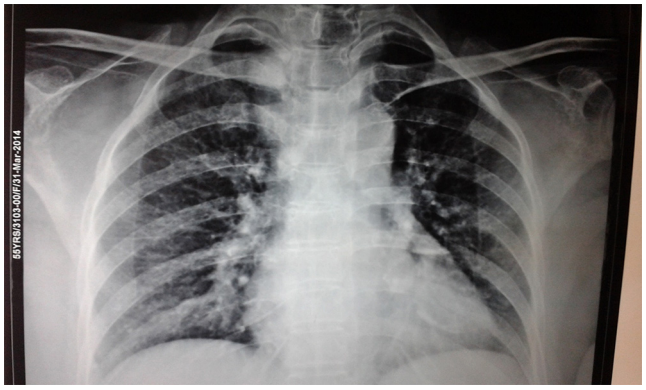


Fig. 1 – Chest X-ray showing sclerotic lesion of the medial end of clavicle.

medial end of clavicle. The patient was sent for fine needle aspiration cytology (FNAC) of the swelling. Histopathology revealed tubercular pathology. The patient was started on anti-tubercular treatment and there was marked improvement with anti-tubercular treatment. The hard swelling disappeared but sclerotic lesion of medial end of clavicle persisted even after 6 months of antitubercular treatment (Fig. 2).

3. Discussion

The occurrence of TB in the flat bones of chest and skull is very rare. With widespread knowledge and awareness of pulmonary TB, unusual sites are becoming a common cause of diagnostic dilemma.[3] However, cases of clavicular or sternoclavicular TB are few. The predilection yields are children, old people, poverty, and immunodeficiency. The clavicle localization is exceptional.[6] Diagnostic problems are confounded by the fact that this site is more prone to the development of neoplasms as compared to infections.[5,7] Fang et al.[5] reported a case of an apparent neoplasm of the medial end of the clavicle in a dialysis patient, which ultimately turned out to be tuberculosis. Osteoarticular TB is almost always secondary to a primary focus elsewhere in the body,[5,8] and a definite attempt should be made to screen the pulmonary, GIT, and renal systems for evidence of disease. The basis for an accurate diagnosis of TB is obtaining representative tissue from the focus or the isolation of Mycobacterium tuberculosis on culture. In our experience with such cases, as well as that of leading workers in this field,[2,4] there is a high incidence of false-negative culture reports. Osteoarticular tuberculosis is a paucibacillary disease in comparison to the number of bacilli seen in pulmonary lesions. This makes demonstration of AFB on staining or on culture from the skeletal lesions extremely difficult. Nevertheless, a determined attempt at culture or staining for AFB is warranted. In most of the cases, however, the diagnosis has to be suspected by clinical features, concomitant pathology, histopathological evidence of granulomatous tissue, and a high index of suspicion.[5,7] TB is thought to be primarily a joint disease, purely bony involvement at an unusual site, with some kind of an sclerotic or destructive radiological picture will bring to mind the more commonly encountered tumors.[9]

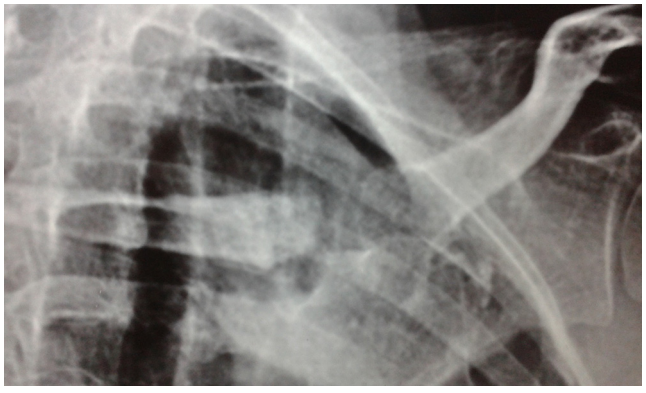


Fig. 2 – Chest X-ray showing sclerotic lesion of medial end of clavicle persisting even after 6-month ATT.

The treatment of skeletal TB is medical, and surgical intervention is needed only for the purpose of obtaining tissue for diagnosis. Once the appropriate anti-TB therapy is started, the symptoms resolve within 6–8 weeks, and most discharging sinuses heal. We recommend a four-drug regimen for a minimum period of 3–4 months, and once the clinical features settle, the patient should be maintained on a two-drug regimen for an additional 9–12 months.

Conflicts of interest

The authors have none to declare.

REFERENCES

1. Verma S, Verma SK, Mehra M. Isolated clavicle bone tuberculosis. *Internet J Orthop Surg.* 2008;8.
2. Tuli SM, Sinha GP. Skeletal tuberculosis "Unusual" lesions. *Indian J Orthop.* 1969;3:5–19.
3. Rasool MN, Govender S. Infections of the clavicle in children. *Clin Orthop.* 1991;265:178–182.
4. Shrivastava KK, Garg LD, Kochar VL. Tuberculosis osteomyelitis of the clavicle. *Acta Orthop Scand.* 1974;45:668–672.
5. Fang JT, Huang CC, Liu HP. Apparent neoplasm of the clavicle of a dialysis patient, ultimately revealed as tuberculosis. *Nephrol Dial Transplant.* 1996;11:1380–1382.
6. Aggarwal AN, Dhammi IK, Singh AP, Kumar S, Goyal MK. Tubercular osteomyelitis of the clavicle: a report of four cases. *J Orthop Surg.* 2009;17:123–126.
7. Abdelwahab IF, Kenan S, Hermann G. Atypical skeletal tuberculosis mimicking neoplasm. *Br J Radiol.* 1991; 64:551–555.
8. Shannon B, Moore M, Houkom J, Waecker Jr NJ. Multifocal cystic tuberculosis of bone. *J Bone Joint Surg.* 1990;72-A: 1089–1092.
9. Basanagoudar PL, Gupta PN, Bahadur R, Dhillon MS. Tuberculosis van de distale clavicula voorkomend als een expansief lytich letsel: een geval. *Acta Orthop Belg.* 2001;67:5.
10. Sy MH, Konate I, Gassama A, Kane A, Sèye SI. Monoarticular/sternoclavicular arthritic tuberculosis: a proposal and an observation. *Int J Tuberc Lung Dis.* 2000;4:486–487.

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: http://www.journals.elsevier.com/indian-journal-of-tuberculosis/

Case Report

Pulmonary artery aneurysm and thrombosis in active tuberculous consolidation

A. Jemshad [a,*], Shameem Ahammed [b], Mansoor C. Abdulla [c], Mohthash Musambil [d]

[a] Assistant Professor, Department of General Medicine, M.E.S. Medical College, Perinthalmanna, Kerala, India
[b] Assistant Professor, Department of Radio Diagnosis, M.E.S. Medical College, Perinthalmanna, Kerala, India
[c] Associate Professor, Department of General Medicine, M.E.S. Medical College, Perinthalmanna, Kerala, India
[d] Molecular Biologist, Assistant Researcher, Central Research Lab, M.E.S. Medical College, Perinthalmanna, Kerala, India

ARTICLE INFO

Article history:
Received 19 November 2014
Accepted 8 July 2015
Available online 9 October 2015

Keywords:
Tuberculosis
Pulmonary artery aneurysm
Thrombus

ABSTRACT

Tuberculosis continues to remain challenging with a variety of complications. We report the case of a 58-year-old female who developed pulmonary artery aneurysm with intra-arterial thrombus as a complication of active tuberculosis. Even though there are reports of pulmonary artery aneurysm in tuberculous cavity, pulmonary artery aneurysm and intra-arterial thrombus in active tuberculosis are very rare.

1. Introduction

Tuberculosis is a major health problem in developing countries with a myriad of presentations and complications. Tuberculosis can lead to pseudoaneurysm, hypercoagulability, increased venous stasis, and endothelial dysfunction, thus increasing the susceptibility to thromboembolism.[1] Our case highlights the occurrence of pulmonary artery aneurysm with intra-arterial thrombus in a patient with pulmonary tuberculosis with no risk factors for thromboembolism, a significant but rare association posing a diagnostic dilemma which may have serious prognostic implications.

2. Case report

A 58-year-old female, known case of Type 2 Diabetes Mellitus and primary billiary cirrhosis, presented with two episodes of hematemesis. She had history of productive cough, low-grade fever and significant weight loss for 2 months. She was fully conscious and oriented, vitals were stable, and had coarse crepitations in the left supraclavicular and infraclavicular regions. The rest of the examination was normal.

Investigations showed Hemoglobin 8.5 gm% (microcytic hypochromic), TC 15,600 cells/c.mm, DC N 71% L 24% M 55%, platelet 2.5 lakhs/c.mm and ESR 71 mm/1st hr. Liver function

* *Corresponding author at*: Department of General Medicine, M.E.S. Medical College, Perinthalmanna, Kerala 679338, India. Tel.: +91 04933 298 300/9846414246; fax: +91 04933 298 300.
E-mail address: jemshadalungal@gmail.com (A. Jemshad).

http://dx.doi.org/10.1016/j.ijtb.2015.09.008

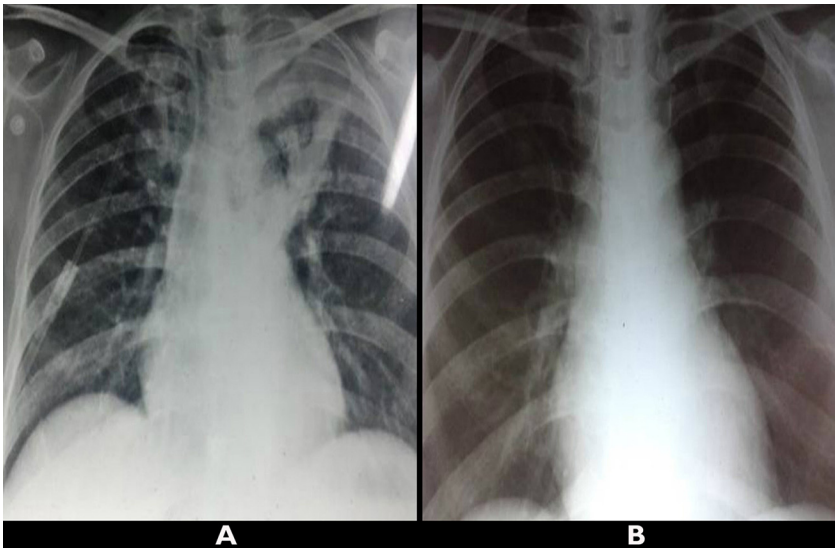


Fig. 1 – Chest X-ray PA view showing Y-shaped linear non-homogenous opacity in the left upper zone (A) as compared to previous X-ray (B).

test showed mildly elevated SGOT and Albumin-Globulin ratio reversal. Renal function tests and urinalysis were all normal. Chest X-ray showed Y-shaped linear non-homogenous opacity in the left upper zone (Fig. 1A). Contrast enhanced CT of thorax showed left upper lobe consolidation, left pulmonary artery aneurysm with intra-arterial thrombus (Fig. 2). Sputum was positive for acid fast bacilli. ANA profile showed positive antimitochondrial antibody. Prothombin time and aPTT were normal. HIV, Hepatitis B, C, IgG and IgM APLA were all negative. Lower limb Doppler showed no evidence of thrombosis. Chest X-ray done three months back was normal (Fig. 1B). USG abdomen showed features of chronic liver disease with portal hypertension. Upper gastrointestinal endoscopy revealed fundal varices and features of portal hypertensive gastropathy (Fig. 3). So a diagnosis of pulmonary artery aneurysm with intra-arterial thrombus secondary to pulmonary tuberculosis, primary billiary cirrhosis with fundal varices was made and was started on antitubercular drugs (levofloxacin, ethambutol, and streptomycin). Glue injection was done for fundal varices. She was not started on anticoagulants, because of hematemesis and patient was not willing for any invasive procedures. Two months later, she had an episode of massive hematemesis and succumbed to her illness.

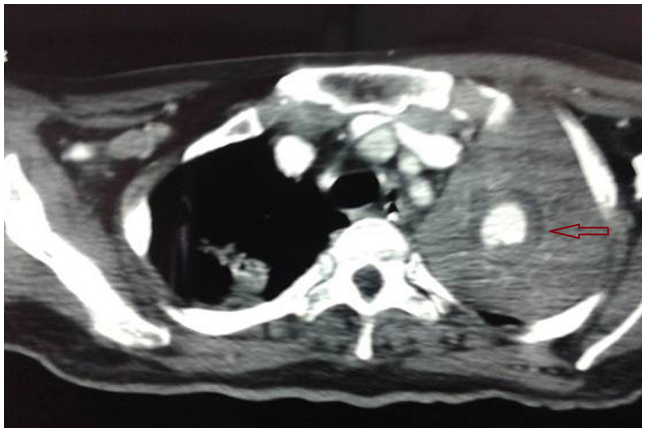


Fig. 2 – Contrast enhanced CT of thorax showing left upper lobe consolidation, left pulmonary artery aneurysm with intra-arterial thrombus.

3. Discussion

Aneurysms of the pulmonary artery are rare in adults. Predisposing conditions include congenital and acquired heart disease, infections (tuberculosis, syphilis), systemic vasculitides (Hughes-Stovin's disease, Behcet's disease), collagen vascular diseases, connective tissue disorders, (Marfan's syndrome, Ehler's-Danlos syndrome) and trauma (direct or blunt chest injury).[2–5]

Inflammatory pulmonary artery aneurysms are an extremely uncommon cause of hemoptysis in pulmonary tuberculosis. Fritz Waldemar Rasmussen, a Danish physician, first described 11 cases of pulmonary aneurysms in patients with tuberculosis in 1868.[6] A destructive pathology in the lung irrespective of the etiology erodes the adjacent structures in the lung. When such a process occurs tangentially across a vessel wall, the media of the vessel is destroyed and thickened intima protrudes out and an aneurysm results. The eponym Rasmussen's aneurysm refers specifically to tuberculous etiology.[7] They are usually peripheral and beyond the branches of main pulmonary artery. Though they are described in tuberculous cavity, our patient had left main pulmonary artery aneurysm in the area of consolidation. Endovascular techniques such as coil embolization, glue embolization, or stent graft placement are the treatment options.

Thrombogenic potential of tuberculosis has been infrequently reported in literature. Deficiency of Antithrombin III, protein C and protein S and elevated plasma fibrinogen levels, increased platelet aggregation seems to induce hypercoagulable

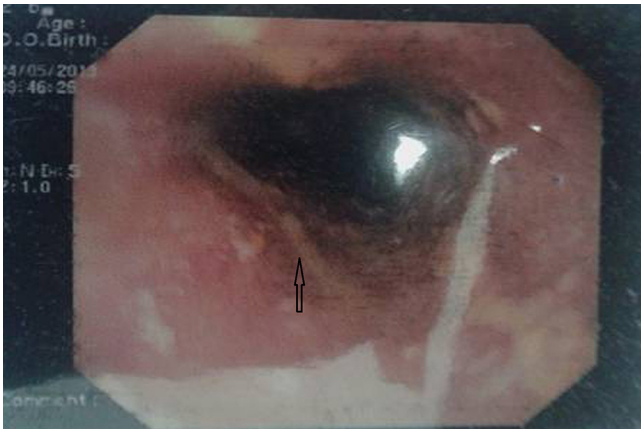


Fig. 3 – Upper gastrointestinal endoscopy showing fundal varices and features of portal hypertensive gastropathy.

state in tuberculosis and improves with treatment.[8] It has also been described that activation of endothelial cells occurs in response to various pathophysiological stimuli resulting in expression of endothelial proteins that change the normally non-thrombogenic internal surface of the vessel to a thrombogenic surface favoring thrombosis.[9] The problem is more in critically ill patients with tuberculosis, because the rate and degree of stimulated platelet aggregation are increased in severe disease, which creates an additional pre-requisite for progression of microthrombogenesis.

These haemostatic changes improve during the first month of ATT,[8] and for this reason, it should be immediately started in addition to anticoagulant therapy. Frequently, a higher dose of warfarin is necessary to achieve therapeutic INR levels, because of rifampin effects on cytochrome P450.

Patients with chronic liver disease are prone for venous thrombosis like deep venous thrombosis and portal vein thrombosis.[10] But they usually present with bleeding manifestation. Chronic liver disease might have contributed in the development of pulmonary thrombosis in our patient.

We report this case because during the literature review, we could not find cases of pulmonary artery aneurysm with intra-arterial thrombus associated with active tuberculous consolidation. The previously reported cases of pulmonary artery aneurysm in patients with tuberculosis were in post-tuberculous cavity.

Conflicts of interest

The authors have none to declare.

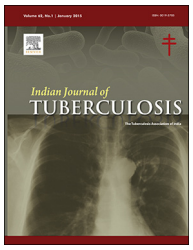
REFERENCES

1. Nkoke C, Bain LE, Jingi AM, Kotta S, Mintom P, Menanga A. Bilateral pulmonary embolism in a patient with pulmonary tuberculosis: a rare association in Yaoundé, Cameroon. *Pan Afr Med J*. 2014;17:262.
2. Deterling RA, Clagett OT. Aneurysms of the pulmonary artery. *Am Heart J*. 1947;34:471.
3. Nestor M. *Radiologic Diagnosis of Disease of the Chest*. Philadelphia: WB Saunders Company; 2001:425–428.
4. Vaideeswar P, Deshpande JR. Pulmonary artery aneurysms. *Int J Cardiol*. 1992;35:424–426.
5. Baum D, Khoury GH, Ongley PA, Swan HJ, Kincaid OW. Congenital stenosis of the pulmonary artery branches. *Circulation*. 1964;29:680–687.
6. Rasmussen V. On haemoptysis, especially when fatal, in its anatomical and clinical aspects. *Edinb Med J*. 1868;14:385–401.
7. Raghuram AR, Kumar S, Balamurughan K, et al. Rasmussen's aneurysm – a brief report. *Indian J Thorac Cardiovasc Surg*. 2005;21:234–235.
8. Turken O, Kunter E, Sezer M, et al. Hemostatic changes in active pulmonary tuberculosis. *Int J Tuberc Lung Dis*. 2002;6:927–932.
9. Lang IM, Mackman N, Kriett JM, Moser KM, Schleef RR. Prothrombic activation of pulmonary arterial endothelial cells in a patient with tuberculosis. *Hum Pathol*. 1996;27:23–27.
10. Senzolo M, Sartori MT, Lisman T. Should we give thromboprophylaxis to patients with liver cirrhosis and coagulopathy? *HPB (Oxford)*. 2009;11:459–464.

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: http://www.journals.elsevier.com/indian-journal-of-tuberculosis/



Case Report

Multidrug-resistant tuberculosis among different types of suspected cases: Study from New Delhi

Ritu Singhal [a], *Neeta Singla* [b], *Vithal Prasad Myneedu* [c,*], *Niti Singh* [d], *Rohit Sarin* [e]

[a] *Specialist Microbiology, Department of Microbiology, National Institute of Tuberculosis and Respiratory Diseases, India*
[b] *Senior Research Officer, Department of Epidemiology, National Institute of Tuberculosis and Respiratory Diseases, India*
[c] *Head of Department, Department of Microbiology, National Institute of Tuberculosis and Respiratory Diseases, India*
[d] *NRL Microbiologist, Department of Microbiology, National Institute of Tuberculosis and Respiratory Diseases, India*
[e] *Director of the Institute, National Institute of Tuberculosis and Respiratory Diseases, India*

ARTICLE INFO

Article history:
Received 30 July 2014
Accepted 8 July 2015
Available online 4 November 2015

Keywords:
Multi-drug resistance
Line probe assay
Mycobacterium

ABSTRACT

There are limited data of multidrug-resistant tuberculosis (MDR-TB) diagnosed in various patient categories by implementing Programmatic Management of Drug Resistant TB (PMDT) using line probe assay (LPA) from our country. Samples from presumptive MDR-TB from five districts of New Delhi were subjected to LPA from 1st October 2011 to 31st December 2014. The MDR-TB diagnosed in 4th & 5th month follow-up positives were significantly higher than other categories of the patients. Only 3/232 (2.2%) RIF resistants were diagnosed among smear negative re-treatment cases. The data suggest interim cost–benefit analysis of the program especially among smear negatives retreatment cases.

1. Introduction

Multidrug-resistant tuberculosis (MDR-TB) defined as the resistance to at-least rifampicin (RIF) and isoniazid (INH) has become a significant public health problem due to prolonged and expensive treatment resulting in failure and death.[1] Based on drug resistance surveillance studies conducted in 2006–2008, estimated proportion of MDR-TB is 2.1% (1.5–2.7%) and 15% (13%–17%), in new and retreatment cases respectively.[2]

India had launched PMDT under Revised National Tuberculosis Control Programme (RNTCP) in 2011, in which notified TB patients are identified as ''presumptive MDR-TB'' based on pre-decided ''Criteria'' and are further diagnosed for MDR-TB by rapid method.[3] Criterion A includes new TB cases smear positive at 5th month of treatment, re-treatment cases smear positive at 4th month, and all TB contacts of diagnosed MDR-TB case. Criterion B includes all smear positive re-treatment PTB cases at diagnosis or follow-up and any smear positive follow-up in Category I (Smear +ve at 2 months of treatment or later) in addition to Criterion A. Criterion C includes all smear negative re-treatment TB cases and HIV-TB co-infected cases, in addition to Criterion B.[3] All RIF resistants are started with category IV treatment irrespective of INH status.

* *Corresponding author at*: HOD Microbiology, National Institute of Tuberculosis and Respiratory Diseases, Aurobindo Marg, New Delhi 110030, India. Tel.: +91 9871731307.
E-mail address: vpm_myn@hotmail.com (V.P. Myneedu).

http://dx.doi.org/10.1016/j.ijtb.2015.09.004

Table 1 – Distribution of suspected and diagnosed multidrug-resistant tuberculosis (MDR-TB) as per Programmatic Management of Drug Resistant TB (PMDT).

Year	Clinical type		Follow up positive at end of 5th month and 4th month, CAT I and CAT II respectively			Follow up positive at end of IP			MDR-TB contacts	CAT II entry smear positive	CAT II entry smear negative	HIV positive	Total
			CAT I, 5th month	CAT II, 4th month	TOTAL	CAT I, end of IP	CAT II, end of IP	Total					
2011	MDR suspects		40	101	141				1				142
	RIF resistance	No.	14	35	49				0				49
		%	35.00%	34.70%	34.50%								34.50%
	MDR	No.	13	30	43				0				43
		%	32.50%	29.70%	30.50%								30.30%
	INH resistance	No.	17	33	50				0				50
		%	42.50%	32.70%	35.50%								35.20%
2012	MDR suspects					800	421	1221	0	1160	47		2430
	RIF resistance	No.				122	60	182	0	175	1		358
		%				15.20%	14.30%	14.90%		15.10%	2.10%		14.70%
	MDR	No.				94	49	143	0	136	1		280
		%				11.80%	11.60%	11.70%		11.70%	2.10%		11.50%
	INH resistance	No.				127	80	207	0	187	1		395
		%				15.90%	19.00%	16.90%		16.10%	2.10%		16.30%
2013	MDR suspects					673	320	993	5	1053	139	11	2201
	RIF resistance	No.				83	38	121	2	168	2	0	293
		%				12.30%	11.90%	12.20%	40.00%	15.60%	1.40%	0	13.30%
	MDR	No.				75	33	108	2	131	2	0	230
		%				11.10%	10.30%	10.90%	40.00%	12.40%	1.40%	0.00%	10.40%
	INH resistance	No.				118	48	166	4	191	4	1	366
		%				17.50%	15.00%	16.70%	80.00%	18.10%	2.90%	9.10%	16.60%
2014	MDR suspects					348	192	540	13	690	46	7	1296
	RIF resistance	No.				41	30	71	4	94	0	2	171
		%				11.80%	15.60%	13.10%	30.80%	13.60%	0.00%	0.00%	13.20%
	MDR	No.				35	20	55	4	72	0	2	133
		%				10.10%	10.40%	10.20%	30.80%	10.40%	0.00%	0.00%	10.30%
	INH resistance	No.				64	38	102	5	140	0	4	251
		%				18.40%	20.00%	18.90%	38.50%	20.30%	0	0	19.40%
Total	MDR suspects		40	101	141	1821	933	2754	18	2903	232	18	6066
	RIF resistance	No.	14	35	49	246	128	374	6	437	3	2	871
		%	35.00%	34.70%	34.50%	13.50%	13.70%	13.60%	33.30%	15.10%	1.30%	11.10%	14.40%
	MDR	No.	13	30	43	210	102	312	6	339	3	2	705
		%	32.50%	29.70%	30.50%	11.50%	10.90%	11.30%	33.30%	11.70%	1.30%	11.10%	11.60%
	INH resistance	No.	17	33	50	309	166	475	9	518	5	5	1062
		%	42.50%	32.70%	35.50%	16.70%	17.80%	17.20%	50.00%	17.80%	2.20%	27.80%	17.50%

MDR-TB: Multi-drug resistant tuberculosis; CAT: Category; RIF: Rifampicin; INH: Isoniazid.

The PMDT introduced line probe assay (LPA), which made MDR-TB detection possible within 48–72 h.[4,5] Though rather expensive, PMDT has established LPA in 45 laboratories across India for MDR-TB with New Delhi amongst the first regions in the country.[3]

There is paucity of data regarding the pattern of MDR-TB diagnosed by implementing PMDT using LPA from our country. Hence, in the present study, data during the study period have been analyzed to compare the MDR-TB obtained between different types of MDR-TB suspects.

2. Material and methods

Samples of all presumptive MDR-TB patients under PMDT from five districts of New Delhi were received in the National Reference Laboratory (NRL) from 1st October 2011 to 31st December 2014 for MDR-TB diagnosis. The study has been approved by institute's ethical committee.

All smear positive processed samples were subjected to LPA after processing as per manufacturer's instructions.[4,5] Smear negative samples were subjected to LPA if culture was positive for *M. tuberculosis*.[6]

For all the patients, data related to type of patient, i.e. end of 5th month (CAT I) or 4th month (CAT II) follow-up positives (FUP), end of intensive phase (IP) treatment, re-treatment entry smear positive or smear negative cases, HIV positive, and MDR-TB contacts were compiled and compared statistically using Fisher's exact test to calculate the level of significance. The MDR-TB diagnosed for various MDR-TB suspects as per criterion A, B or C was also recorded.

3. Results

Total of 6066 samples from presumptive MDR-TB patients were received in the laboratory during the study period. Overall, proportion of MDR-TB cases diagnosed were 705/6066 (11.6%). Of these, MDR-TB among presumptive MDR-TB patients were, 30.3%, 15.3% and 10.4% in criterion A, B and C, respectively. The details are provided in Table 1.

The MDR-TB obtained among 5th and 4th month FUP of CAT 1 and CAT II respectively was not significantly different. The difference in MDR-TB obtained among FUP at 4th/5th month and between FUP at end of IP and retreatment cases at entry was significant (P value for both <0.0001). MDR-TB at end of IP cases and retreatment cases at entry was similar (P value = 0.7). Only 3 (2.2%) smear negative retreatment cases were found, which were significantly less than smear positive. High proportion of MDR 6/18 (33.3%) was found in MDR-TB contacts. In HIV cases, MDR-TB was 11.1%, not significantly different from retreatment or FUP cases at end of IP.

4. Discussion

In Indian studies conducted over last decade, MDR-TB rates are reported from 17.4% to 58.2%.[7–9] Prasad et al. found high MDR-TB of 58.2%, possibly due to treatment failures among smear positives at later month, as seen in similar category in present study. Hanif et al. and Ramachandran et al. reported 47.1% and 17.4%, MDR-TB among any retreatment cases respectively.[7,9] Higher rate in study by Hanif et al. could be possibly due to selection bias involved. In the current study, MDR-TB among re-treatment cases is in 11.7%.

In the present study, an interesting observation found was significantly higher MDR-TB in 4th or 5th month FUP cases as compared to FUP cases at end of IP or retreatment smear positive cases at entry. Possibly the reason of patients having higher likelihood of MDR-TB among those who continue to be AFB smear positive at 4th/5th month during the treatment could be that the bacteria having mutations would be selected, multiplied, and hence detected, which is less likely at end of initial months or start of therapy. Also, before implementation of LPA in 4th quarter 2011, there could have been pool of undiagnosed MDR-TB cases which has added to the high rate of RIF resistance.

There was statistically significant difference between MDR-TB obtained between smear positive retreatment cases and smear negative retreatment cases as only three MDR-TB patients were diagnosed in the later category. The low MDR-TB rate undermines the cost-effectiveness and logistics of using culture followed by LPA for such cases. Use of Xpert could increase the case detection of MDR-TB in smear negatives as reported.[10]

MDR-TB was found to be significantly high among suspects based on history of contact with MDR-TB case, which calls for the role of newer technologies in rapid MDR-TB case detection and immediate start of treatment in order to contain the disease. Also, studies based on epidemiological typing of MDR-TB cases and contacts should be executed for determining the spread. One limitation of the study is very less numbers of MDR-TB contacts and HIV-TB cases.

5. Conclusion

This is an attempt in the country to analyze and compare the MDR-TB obtained between different types of MDR-TB suspects in PMDT. The finding among smear negative cases endorses the decision of RNTCP for deployment of Xpert across the country in order to enhance case detection among such cases. Need of the hour is the generation of MDR-TB detection data by Xpert in this group across different centers.

Conflicts of interest

The authors have none to declare.

Acknowledgements

We acknowledge the help of the FIND data entry operator and FIND technicians in entering the line probe assay data.

REFERENCES

1. Centre for Disease Control (CDC). Emergence of *Mycobacterium tuberculosis* with extensive resistance to second line drugs-world-wide 2000-2004. *Morb Mortal Wkly Rep MMWR*. 2006;55:301–305.
2. Revised National Tuberculosis Control Programme, RNTCP. *Annual Status report. Central Tuberculosis Division (CTD), Directorate General of Health Services*. New Delhi, India: Ministry of Health and Family Welfare; 2012.
3. Revised National Tuberculosis Control Programme, RNTCP. *Guidelines on Programmatic Management of Drug Resistant TB (PMDT) in India*. New Delhi, India: Central Tuberculosis Division (CTD), Directorate General of Health Services, Ministry of Health and Family Welfare; 2012.
4. Rodrigues C, Shenai S, Sadani M, et al. Evaluation of the BACTEC MGIT 960 TB system for recovery and identification of *Mycobacterium tuberculosis* complex in a high volume tertiary care centre. *Indian J Med Microbiol*. 2009;27(3):217–221.
5. Singhal R, Arora J, Lal P, Bhalla M, Myneedu VP, Behera D. Comparison of line probe assay with liquid culture for rapid detection of multi-drug resistance in *Mycobacterium tuberculosis*. *Indian J Med Res*. 2012;136:31–34.
6. Kent PT, Kubica GP. *Public Health Mycobacteriology, A guide for level III Laboratory*. Atlanta, GA: Public Health Services, Center for Disease Control; 1985.
7. Ramachandran R, Nalini S, Chandershekhar V, et al. Surveillance of drug resistant tuberculosis in the state of Gujrat, India. *Int J Tuberc Lung Dis*. 2009;134(9):1154–1160.
8. Prasad R, Jain A, Anand SC, et al. A five year study of drug susceptibility testing pattern of Mycobacterium tuberculosis isolates from patients of category II failure of pulmonary tuberculosis under DOTS, (Directly Observed Treatment, Short Course) from Northern India. *Am J Respir Crit Care Med*. 2010;181:A5470.
9. Hanif M, Malik S, Dhingra VK. Acquired drug resistance pattern in tuberculosis cases at the State Tuberculosis Centre, Delhi, India. *Int J Tuberc Lung Dis*. 2009;13:74–78.
10. Raizada N, Sachdeva KS, Nair SA, et al. Enhancing TB Case Detection: Experience in offering upfront Xpert MTB/RIF testing to pediatric presumptive TB and DR TB cases for early rapid diagnosis of drug sensitive and drug resistant TB. *PLoS One*. 2014;20(9(8)).

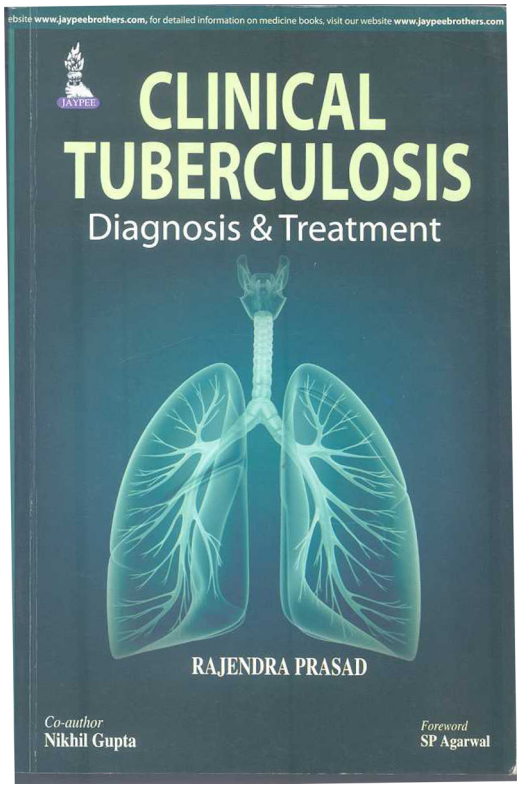
Available online at www.sciencedirect.com

ScienceDirect

journal homepage: http://www.journals.elsevier.com/indian-journal-of-tuberculosis/

Book Review

Rajendra Prasad, Nikhil Gupta, Clinical Tuberculosis – Diagnosis and Treatment, Jaypee Brothers Medical Publishers (P) Ltd., New Delhi, India (2015).



The book "Clinical Tuberculosis – Diagnosis and Treatment", written under 50 heads, practically covers all aspects of tuberculosis, ranging from Landmarks in Tuberculosis Treatment to Infection Control in Tuberculosis. Colour plates have also been provided for enhancing visual knowledge in tuberculosis. There has been inclusion of different newer modes of investigation under diagnostic techniques in tuberculosis, including utility of fibreoptic bronchoscopy in diagnosis of sputum negative cases. Details of anti-TB drugs have been covered in two chapters along with their mechanism of action and side/toxic effects. Basic concepts in treatment of tuberculosis, such as role of special diet, rest, Fixed Dose Combinations (FDC) and controversial topics like daily *versus* intermittent regimen, have been extensively discussed.

This book also carries two chapters where 'case-based management' has been discussed. "Tuberculosis in elderly" with emphasis on pathogenesis has been discussed in a chapter. Infection control strategies in tuberculosis and multidrug resistant TB along with drug rehabilitation have been discussed in detail.

The book could have been further enriched by addition of chapters on new vaccines, vaccination strategy and the need for inclusion of sociological aspects in treatment of tuberculosis.

The book is recommended for undergraduate and postgraduate students and should be helpful as an accompaniment for advancement of knowledge in tuberculosis in institution libraries.

V.K. Arora
Executive Editor, IJT, India
E-mail address: vijaykumar1945@gmail.com

Available online 4 November 2015

http://dx.doi.org/10.1016/j.ijtb.2015.09.006
0019-5707/

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: http://www.journals.elsevier.com/indian-journal-of-tuberculosis/

Abstracts

Performance of a novel algorithm using automated digital microscopy for diagnosing tuberculosis

Nazir A. Ismail; Shaheed V. Omar; James J. Lewis; David W. Dowdy; Andries W. Dreyer; Hermina van der Meulen; George Nconjana; David A. Clark; Gavin J. Churchyard. *American Journal of Respiratory and Critical Care Medicine* 2015; **191(12):** 1352–3.

Rationale: TBDx automated microscopy is a novel technology that processes digital microscopic images to identify acid-fast bacilli (AFB). Use of TBDx as part of a diagnostic algorithm could improve the diagnosis of tuberculosis (TB), but its performance characteristics have not yet been formally tested.

Objectives: To evaluate the performance of the TBDx automated microscopy system in algorithms for diagnosis of TB.

Methods: Prospective samples from patients with presumed TB were processed in parallel with conventional smear microscopy, TBDx microscopy, and liquid culture. All TBDx-positive specimens were also tested with the Xpert MTB/RIF (GXP) assay. We evaluated the sensitivity and specificity of two algorithms—(1) TBDx-GXP (TBDx with positive specimens tested by Xpert MTB/RIF) and (2) TBDx alone—against the gold standard liquid media culture.

Measurements and main results: Of 1210 samples, 1009 were eligible for evaluation, of which 109 were culture positive for *Mycobacterium tuberculosis*. The TBDx system identified 70 specimens (68 culture positive) as having 10 or more putative AFB (high positive) and 207 (19 culture positive) as having 1–9 putative AFB (low positive). An algorithm in which ''low-positive'' results on TBDx were confirmed by GXP had 78% sensitivity (85 of 109) and 99.8% specificity (889 of 900), requiring 21% (207 of 1,009) specimens to be processed by GXP. As a stand-alone test, a ''high-positive'' result on TBDx had 62% sensitivity and 99.7% specificity.

Conclusions: TBDx used in diagnostic algorithms with GXP provided reasonable sensitivity and high specificity for active TB while dramatically reducing the number GXP tests performed. As a stand-alone microscopy system, its performance was equivalent to that of a highly experienced TB microscopist.

http://dx.doi.org/10.1016/j.ijtb.2015.09.013

Prevalence of tuberculosis in Faridabad district, Haryana State, India

SK Sharma; Ashish Goel; SK Gupta; Krishna Mohan; V Sreenivas; SK Rai; UB Singh; LS Chauhan. *Indian Journal of Medical Research* 2015; **141(2):** 228–35.

Background and objectives: Epidemiological information on tuberculosis (TB) has always been vital for planning control strategies. It has now gained further importance for monitoring the impact of interventions to control the disease. The present study was done to estimate the prevalence of bacillary tuberculosis in the district of Faridabad in Haryana State of India among persons aged older than 15 years.

Methods: In this cross-sectional study, residents of Faridabad district were assessed for the prevalence of tuberculosis. Twelve rural and 24 urban clusters with estimated populations of 41,106 and 64,827 individuals were selected for the study. Two sputum samples were collected from individuals found eligible for inclusion. The samples were also cultured by modified Petroff's method and were examined for growth of*Mycobacterium tuberculosis* once a week for eight weeks. A person found positive by smear and/or culture was identified as sputum-positive pulmonary TB positive.

Results: A total of 105,202 subjects were enumerated in various clusters of the Faridabad district. There were 50,057 (47.58%) females and 55,145 (52.42%) males. Of these 98,599 (93.7%) were examined by the study group (47,976 females; 50,623 males). The overall prevalence of sputum smear or culture positive pulmonary tuberculosis in our study was found to be 101.4 per 100,000 population.

Interpretation and conclusions: The present results showed that the prevalence of sputum positive pulmonary tuberculosis was higher in Faridabad district than the notification rates recorded by the World Health Organization for the contemporary period, a disparity that could be explained by a difference in case detection strategy employed for the study.

http://dx.doi.org/10.1016/j.ijtb.2015.09.014

High and equitable tuberculosis awareness coverage in the community-driven Axshya TB control project in India

B. Thapa; S.S. Chadha; A. Das; S. Mohanty; J. Tonsing. *Public Health Action* 2015; **5(1)**: 70–3.

Data from surveys on knowledge, attitudes and practice (KAP) on tuberculosis (TB) conducted under the Axshya project at two time points (baseline 2010–2011 and mid-line 2012–2013) were analysed for changes in coverage and equity of TB awareness after project interventions. Overall coverage increased from 84% at baseline to 88% at midline (5% increase, $P < 0.05$). In comparison to baseline results, coverage at the midline survey had significantly increased, from 81% to 87% among the rural population, from 81% to 86% among women, from 73% to 85% in the ≥55 years age group, from 71% to 80% among

illiterates and from 73% to 81% in the south zone ($P < 0.05$). The equity gap among the different study groups (settlement, sex, age, education and zones) decreased from 6–23% at baseline to 3–11% during the midline survey. The maximum decline was observed for type of settlement (rural vs. urban), from 10% to 3% ($P < 0.05$). This community-driven TB control project has achieved high and equitable coverage of TB awareness, offering valuable lessons for the global community.

http://dx.doi.org/10.1016/j.ijtb.2015.09.015

Utility of adenosine deaminase (ADA), PCR & thoracoscopy in differentiating tuberculous & non-tuberculous pleural effusion complicating chronic kidney disease

Sravan Kumar; Ritesh Agarwal; Amanjit Bal; Kusum Sharma; Navneet Singh; Ashutosh N Aggarwal; Indu Verma; Satyawati V. Rana; Vivekanand Jha. *Indian Journal of Medical Research* 2015; **141(3):** 308–14.

Background and objectives: Pleural effusion is a common occurrence in patients with late-stage chronic kidney disease (CKD). In developing countries, many effusions remain undiagnosed after pleural fluid analysis (PFA) and patients are empirically treated with antitubercular therapy. The aim of this study was to evaluate the role of adenosine deaminase (ADA), nucleic acid amplification tests (NAAT) and medical thoracoscopy in distinguishing tubercular and non-tubercular aetiologies in exudative pleural effusions complicating CKD.
Methods: Consecutive stage 4 and 5 CKD patients with pleural effusions underwent PFA including ADA and PCR [65 kDa gene; multiplex (IS6110, protein antigen b, MPB64)]. Patients with exudative pleural effusion undiagnosed after PFA underwent medical thoracoscopy.
Results: All 107 patients underwent thoracocentesis with 45 and 62 patients diagnosed as transudative and exudative pleural effusions, respectively. Twenty-six of the 62 patients underwent medical thoracoscopy. Tuberculous pleurisy was diagnosed in six while uraemic pleuritis was diagnosed in 20 subjects. The sensitivity and specificity of pleural fluid ADA, 65 kDa gene PCR, and multiplex PCR were 66.7 and 90 per cent, 100 and 50 per cent, and 100 and 100 per cent, respectively. Thoracoscopy was associated with five complications in three patients.
Interpretation and conclusions: Uraemia remains the most common cause of pleural effusion in CKD even in high TB prevalence country. Multiplex PCR and thoracoscopy are useful investigations in the diagnostic work-up of pleural effusions complicating CKD while the sensitivity and/or specificity of ADA and 65 kDa gene PCR is poor.

http://dx.doi.org/10.1016/j.ijtb.2015.09.016

MDR-TB screening in a setting with molecular diagnostic techniques: Who got tested, who didn't and why?

H.D. Shewade; S. Govindarajan; B.N. Sharath; J.P. Tripathy; P. Chinnakali; A.M.V. Kumar; M. Muthaiah; K. Vivekananda; A.K. Paulraj; G. Roy. *Public Health Action* 2015; **5(2):** 132–9.

Setting: The Revised National Tuberculosis Control Programme, Puducherry, India, which has facilities for molecular diagnostic technique.
Objective: To determine pre-diagnostic and pre-treatment attrition among presumptive multidrug-resistant tuberculosis (MDR-TB) patients and reasons for attrition.
Methods: In this mixed-methods study, the quantitative component consisted of retrospective cohort analysis through record review of all presumptive MDR-TB patients recorded between October 2012 and September 2013. The qualitative component included in-depth interviews with key informants involved in programmatic management of drug-resistant tuberculosis services.
Results: Of 341 eligible presumptive MDR-TB patients, pre-diagnostic and pre-treatment attrition was respectively 45.5% (155/341) and 29% (2/7). Patients with extra-pulmonary TB (RR = 2.3), those with human immuno-deficiency and TB co-infection (RR = 1.7), those registered during October–December 2012 (RR = 1.3) and those identified from primary/secondary health centres (RR = 1.8) were less likely to be tested. Themes that emerged during the analysis of the qualitative data were 'lack of a systematic mechanism to track referrals for culture and drug susceptibility testing', 'absence of courier service to transport sputum', 'lack of knowledge and ownership among staff of general health system', 'shortage of diagnostic kits' and 'patient non-adherence'.
Conclusion: Despite the introduction of molecular diagnostic techniques, operational issues in MDR-TB screening remain a concern and require urgent attention.

http://dx.doi.org/10.1016/j.ijtb.2015.09.017

Adverse drug reactions in management of multi drug resistant tuberculosis, in tertiary chest institute

J. Akshata; A. Chakrabarthy; R. Swapna; S. Buggi; M. Somashekar. *Journal of Tuberculosis Research* 2015; **3(2):** 27–33. http://dx.doi.org/10.4236/jtr.2015.32004.

Background: Multidrug resistant tuberculosis is a global threat. Effective treatment is implemented as per RNTCP guidelines. But the drugs used have great potential to develop adverse drug reactions. Such drug reactions if not managed optimally can lead to unfavourable treatment outcome. Hence, the study is to know the occurrence of adverse drug reactions.
Aims: To study the occurrence of adverse drug reactions in treatment of multidrug resistant tuberculosis and hence the factors affecting the treatment.
Settings and design: Retrospective analysis of patients treated with standardised regimen for MDR-TB, as per RNTCP guidelines at a tertiary chest institute between august 2011 and December 2014.
Methods and material: Retrospective analysis of 607 patients' records reviewed for the occurrence of adverse drug reactions. All adverse reactions are noted and diagnosed either clinically or by laboratory evidence.
Results: Among the 607 patients included in the study, majority had one or more adverse drug reactions. The most common was gastritis (71.7%), which was easily treatable, and the least common was visual impairment (0.2%). Only 1.7% discontinued the treatment citing adverse drug reactions and 10.5% required permanent discontinuation of the offending drug.
Conclusion: Treatment of MDR-TB is challenging mainly due to the long duration of treatment and the potential adverse reactions of the drugs used. These reactions are frequent but majority of them can be successfully managed without treatment interruption. Training the peripheral health centre workers to identify and refer the patients with adverse reaction bears a major impact on treatment outcome.

http://dx.doi.org/10.1016/j.ijtb.2015.09.018

High effectiveness of a 12-month regimen for MDR-TB patients in Cameroon

C. Kuaban; J. Noeske; H.L. Rieder; N. Aït-Khaled; J.L. Abena Foe; A. Trébucq. *The International Journal of Tuberculosis and Lung Disease* 2015; **19(5):** 517–24.

Setting: Two specialised multidrug-resistant tuberculosis (MDR-TB) treatment units in Cameroon.

Objective: To assess outcome and adverse drug events with a standardised 12-month regimen for MDR-TB among second-line drug naïve patients.

Design: Prospective observational study of MDR-TB patients treated with a standardised 12-month regimen including gatifloxacin, clofazimine, prothionamide, ethambutol and pyrazinamide throughout, supplemented by kanamycin and isoniazid during an intensive phase of a minimum of 4 months. Progress was monitored monthly until treatment completion and twice over one year after treatment cessation.

Results: Eighty-seven potentially eligible patients were lost and never treated due to delayed availability of test results. Among the 150/236 eligible and treated patients, 134 (89%) successfully completed treatment, 10 died, 5 were lost, 1 failed and none relapsed. The patients' mean age was 33.7 years (range 17–68), 73 (49%) were females, 120 (80%) had failed on previous treatment, 30 (20%) were human immunodeficiency virus seropositive, 62 (43%) had a body mass index <18.5 kg/m^2 and 41 (27%) had radiographic involvement of five or six of the six lung zones. The most important adverse drug event was hearing impairment, which occurred in 46 of 106 (43%) patients.

Conclusions: These results add further evidence for the usefulness of shorter, standardised regimens among patients without second-line drug resistance.

http://dx.doi.org/10.1016/j.ijtb.2015.09.019

Follow-up examinations: Are multidrug-resistant tuberculosis patients in Uttar Pradesh, India, on track?

U.C. Tripathi; S.B. Nagaraja; J.P. Tripathy; S.K. Sahu; M. Parmar; K. Rade; S. Bhatnagar; A. Ranjan; K.S. Sachdeva. *Public Health Action* 2015; **5(1):** 59–64.

Setting: All multidrug-resistant tuberculosis (MDR-TB) patients who had completed 6 months of treatment under the Revised National Tuberculosis Control Programme (RNTCP) in Uttar Pradesh, the largest state in northern India.

Objective: To determine the proportion of MDR-TB patients with regular follow-up examinations, and underlying provider and patient perspectives of follow-up services.

Methods: A retrospective cohort study was undertaken involving record reviews of 64 eligible MDR-TB patients registered during April–June 2013 in 11 districts of the state. Patients and programme personnel from the selected districts were interviewed using a semi-structured questionnaire.

Results: A total of 34 (53.1%) patients underwent follow-up sputum culture at month 3, 43 (67.2%) at month 4, 36 (56.3%) at month 5 and 37 (57.8%) at month 6. Themes associated with irregular follow-up that emerged from the interviews were multiple visits, long travel distances, shortages of equipment at the facility and lack of knowledge among patients regarding the follow-up schedule.

Conclusion: The majority of the MDR-TB patients had irregular follow-up visits. Provider-related factors outweigh patient-related factors on the poor follow-up examinations. The programme should focus on the decentralisation of follow-up services and ensure logistics and patient-centred counselling to improve the regularisation of follow up.

http://dx.doi.org/10.1016/j.ijtb.2015.09.020

Childhood tuberculosis and exposure to indoor air pollution: A systematic review and meta-analysis

N. Jafta; P.M. Jeena; L. Barregard; R.N. Naidoo. *The International Journal of Tuberculosis and Lung Disease* 2015; **19(5):** 596–602.

Background: Indoor air pollution (IAP) from environmental tobacco smoke (ETS) and biomass fuel smoke (BMS) poses respiratory health risks, with children and women bearing the major burden.

Objectives: We used a systematic review and meta-analysis to investigate the relation between childhood tuberculosis (TB) and exposure to ETS and BMS.

Methods: We searched three databases for epidemiological studies that investigated the association of childhood TB with exposure to ETS and BMS. We calculated pooled estimates and heterogeneity for studies eligible for inclusion in the meta-analysis and stratified studies on ETS by outcome.

Results: Five case-control and three cross-sectional studies were eligible for inclusion in the meta-analysis and quality assessment. Pooled effect estimates showed that exposure to ETS is associated with tuberculous infection and TB disease (OR 1.9, 95%CI 1.4–2.9) among exposed compared to non-exposed children. TB disease in ETS studies produced a pooled OR of 2.8 (95%CI 0.9–4.8), which was higher than the OR for tuberculous infection (OR 1.9, 95%CI 0.9–2.9) for children exposed to ETS compared to non-exposed children. Studies on BMS exposure were too few and too small to permit a conclusion.

Conclusion: Exposure to ETS increases the risk of childhood TB disease or tuberculous infection.

http://dx.doi.org/10.1016/j.ijtb.2015.09.021

Could repeated prevalence surveys lead to decreasing tuberculosis prevalence in a community?

R. Subramani; C. Kolappan; V. Chandrasekaran; N. Selvakumar; F. Wares; D. Baskaran; S. Swaminathan. *The International Journal of Tuberculosis and Lung Disease* 2015; **19(6):** 635–9.

Setting: Tiruvallur District, South India, where one baseline tuberculosis (TB) disease prevalence survey followed by three repeat prevalence surveys were conducted every 2.5 years between 1999 and 2008, and where the DOTS strategy was implemented in 1999.

Objective: To rule out the possibility that the observed decline in TB prevalence was influenced by conducting repeat prevalence surveys, we compared the findings from two surveys: the third repeat survey conducted in 2006–2008 and an independent single survey in a neighbouring area conducted in 2008–2009.

Design: An independent survey was conducted to estimate the prevalence of TB in the same district in 2008–2009 using a different set of villages and employing repeat survey methodology. The independent survey findings were compared with those of the third repeat survey.

Results: The estimated prevalence rate of culture- and smear-positive TB was respectively 401 per 100,000 and 186 per 100,000 population in the third repeat survey area. The corresponding rates were 340 and 184/100,000 in the independent survey area. The difference in prevalence was not significant (culture $P = 0.09$; smear $P = 0.93$).

Conclusion: The estimated prevalence rates in the two different sample survey areas were comparable, indicating that the repeated prevalence surveys in the study area did not influence the observed decline in TB disease prevalence.

http://dx.doi.org/10.1016/j.ijtb.2015.09.022

Cost-utility analysis of LED fluorescence microscopy in the diagnosis of pulmonary tuberculosis in Indian settings

V. Kelly; K.D. Sagili; S. Satyanarayana; L.W. Reza; S.S. Chadha; N.C. Wilson. *The International Journal of Tuberculosis and Lung Disease* 2015; **19(6)**: 696–701.

Background: With support from the Stop TB Partnership's TB REACH Wave 2 Grant, diagnostic microscopy services for tuberculosis (TB) were upgraded from conventional Ziehl-Neelsen (ZN) based sputum microscopy to light emitting diode technology-based fluorescence microscopy (LED FM) in 200 high-workload microscopy centres in India as a pilot intervention.

Objective: To evaluate the cost-effectiveness of LED-FM over conventional ZN microscopy to inform further scale-up.

Methods: A decision-tree model was constructed to assess the cost utility of LED FM over ZN microscopy. The results were summarised using incremental cost-effectiveness ratio (ICER); one-way and probabilistic sensitivity analyses were also conducted to address uncertainty within the model. Data were analysed from 200 medical colleges in 2011 and 2012, before and after the introduction of LED microscopes. A full costing analysis was carried out from the perspective of a national TB programme.

Results: The ICER was calculated at US$14.64 per disability-adjusted life-year, with an 82% probability of being cost-effective at a willingness-to-pay threshold equivalent to Indian gross domestic product per capita.

Conclusions: LED FM is a cost-effective intervention for detecting TB cases in India at high-workload medical college settings.

http://dx.doi.org/10.1016/j.ijtb.2015.09.023

Quality of tuberculosis care in India: A systematic review

S. Satyanarayana; R. Subbaraman; P. Shete; G. Gore; J. Das; A. Cattamanchi; K. Mayer; D. Menzies; A.D. Harries; P. Hopewell; M. Pai. *The International Journal of Tuberculosis and Lung Disease* 2015; **19(7):**751–63.

Background: While Indian studies have assessed care providers' knowledge and practices, there is no systematic review on the quality of tuberculosis (TB) care.

Methods: We searched multiple sources to identify studies (2000–2014) on providers' knowledge and practices. We used the International Standards for TB Care to benchmark quality of care.

Results: Of the 47 studies included, 35 were questionnaire surveys and 12 used chart abstraction. None assessed actual practice using standardised patients. Heterogeneity in the findings precluded meta-analysis. Of 22 studies evaluating provider knowledge about using sputum smears for diagnosis, 10 found that less than half of providers had correct knowledge; 3 of 4 studies assessing self-reported practices by providers found that less than a quarter reported ordering smears for patients with chest symptoms. In 11 of 14 studies that assessed treatment, less than one third of providers knew the standard regimen for drug-susceptible TB. Adherence to standards in practice was generally lower than correct knowledge of those standards. Eleven studies with both public and private providers found higher levels of appropriate knowledge/practice in the public sector.

Conclusions: Available evidence suggests suboptimal quality of TB care, particularly in the private sector. Improvement of quality of care should be a priority for India.

http://dx.doi.org/10.1016/j.ijtb.2015.09.024

RMP exposure is lower in HIV-infected TB patients receiving intermittent than daily anti-tuberculosis treatment

A.K. Hemanth Kumar; G. Narendran; R.S. Kumar; G. Ramachandran; L. Sekar; K. Raja; S. Swaminathan. *The International Journal of Tuberculosis and Lung Disease* 2015; **19(7):** 805–7.

We compared the pharmacokinetics of rifampicin (RMP) during daily and intermittent (thrice weekly) anti-tuberculosis treatment in human immunodeficiency virus infected tuberculosis patients. Patients treated with a thrice-weekly regimen had significantly lower plasma peak concentration, area under the time concentration curve from 0 to 24 h and higher oral clearance of RMP than those treated with the daily regimen. The median values were respectively 3.7 and 6.4 μg/ml ($P < 0.001$), 20.7 and 29.4 μg/ml h ($P = 0.03$) and 21.7 and 15.3 ml/min ($P = 0.03$).

http://dx.doi.org/10.1016/j.ijtb.2015.09.025

Xpert MTB/RIF assay for the diagnosis of pulmonary tuberculosis in children: A systematic review and meta-analysis

Anne K. Detjen; Andrew R. DiNardo; Jacinta Leyden; Karen R. Steingart; Dick Menzies; Ian Schiller; Nandini Dendukuri; Anna M. Mandalakas. *The Lancet Respiratory Medicine* 2015; **3(6):** 415–96.

Background: Microbiological confirmation of childhood tuberculosis is rare because of the difficulty of collection of specimens, low sensitivity of smear microscopy, and poor access to culture. We aimed to establish summary estimates for sensitivity and specificity of the Xpert MTB/RIF assay compared with microscopy in the diagnosis of pulmonary tuberculosis in children.

Methods: We searched for studies published up to January 6, 2015, that used Xpert in any setting in children with and without HIV infection. We systematically reviewed studies that compared the diagnostic accuracy of Xpert MTB/RIF (Xpert) with microscopy for detection of pulmonary tuberculosis and rifampicin resistance in children younger than 16 years against two reference standards—culture results and culture-negative children who were started on anti-tuberculosis therapy. We did meta-analyses using a bivariate random-effects model.

Findings: We identified 15 studies including 4768 respiratory specimens in 3640 children investigated for pulmonary tuberculosis. Culture tests were positive for tuberculosis in 12% (420 of 3640) of all children assessed and Xpert was positive in 11% (406 of 3640). Compared with culture, the pooled sensitivities and specificities of Xpert for tuberculosis detection were 62% (95% credible interval 51–73) and 98% (97–99), respectively, with use of expectorated or induced sputum samples and 66% (51–81) and 98% (96–99), respectively, with use of samples from gastric lavage. Xpert sensitivity was 36–44% higher than was sensitivity for microscopy. Xpert sensitivity in culture-negative children started on antituberculosis therapy was 2% (1–3) for expectorated or induced sputum.

Xpert's pooled sensitivity and specificity to detect rifampicin resistance was 86% (95% credible interval 53–98) and 98% (94–100), respectively.
Interpretation: Compared with microscopy, Xpert offers better sensitivity for the diagnosis of pulmonary tuberculosis in children and its scale-up will improve access to tuberculosis diagnostics for children. Although Xpert helps to provide rapid confirmation of disease, its sensitivity remains suboptimum compared with culture tests. A negative Xpert result does not rule out tuberculosis. Good clinical acumen is still needed to decide when to start antituberculosis therapy and continued research for better diagnostics is crucial.
Funding: WHO, Global TB Program of Texas Children's Hospital.

http://dx.doi.org/10.1016/j.ijtb.2015.09.026