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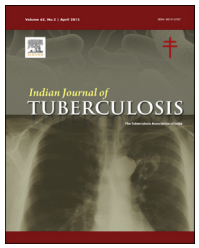

Editorial

Implementing the End TB Strategy: Well begun will be half done

A new chapter was opened in the history of tuberculosis (TB) on 19 May 2014. On that day, the delegates attending the Sixty-seventh World Health Assembly (WHA) in Geneva resolved to see an end to the global TB epidemic over the next two decades.[1] Ending the TB epidemic, as explained in the "Global strategy and targets for tuberculosis prevention, care and control after 2015" adopted by the WHA, means reducing the levels of TB in the whole world to those attained by many rich countries where TB is no longer a major public health problem.[2] The global strategy sets ambitious targets for 2035: reducing TB deaths in the world by 95% and reducing TB incidence rate in the world by 90%, amounting to less than ten TB cases occurring per 100,000 population per year. Making a departure from the practice of focussing only on the disease burden to monitoring progress, this strategy also sets a third target of eliminating catastrophic costs due to TB for the affected families. This target, expected to be met much sooner – by 2020 – will be a dual measure of alleviating socioeconomic suffering due to TB and enhancing equity in access to TB care and prevention. Milestones to be achieved at every five-year interval have also been delineated, including for the important year of 2030, the expected end-date for the Sustainable Development Goals under formulation. The new strategy, that replaces the Stop TB Strategy meant for the period 2006–2015, is called the "End TB Strategy". Panel 1 presents the End TB Strategy including its vision, goal, milestones and targets.

The inclusive process of making of the End TB Strategy that reflects the perspectives of a wide range of stakeholders and sets ambitious targets has been both inspiring and challenging.[3] The process of translating the global strategy into national policies and plans and their implementation on the ground in diverse country-settings could be challenging still. Nevertheless, the possibility of prevailing over a top infectious killer that afflicts the poor the most make these challenges worth meeting. Although the strategy kicks off formally in 2016, the journey has already begun. The first big step of the national health ministers and their representatives endorsing the global strategy and targets has been taken. Work must begin now to prepare for the implementation of a new and demanding strategy. A sound start is key to producing required results.

The End TB Strategy is a strategy with difference. It rests on three pillars – so called to signify that they are equally important. The first pillar significantly enhances the TB care and support component and, importantly, adds TB prevention to it. Scaled up implementation of the expanded catalogue of core TB-specific interventions listed under the first pillar will be possible only if it is backed up by strengthened systems and pertinent policies listed under the second pillar. For example, ensuring early diagnosis and notification of all people with TB will require policies and systems to undertake outreach and secure engagement of all public and private care providers. Similarly, universal access to care and support for all people with TB will materialize only if they are an integral part of national policies on universal health coverage and social protection. Furthermore, policies and systems enabling linkages with other health, social sector, and development programmes will also be essential for implementing several components of the strategy including, for instance, managing co-morbidities, infection control, and addressing social determinants of TB. The third pillar is equally critical. It is meant to boost research for discovery, development and uptake of new tools without which the goal of ending the TB epidemic may not realise. It is also meant to promote continuing operational research for country-specific and context-specific adaptations of and innovations to the strategy before and after it is scaled up.

Clearly, this judicious mix of biomedical and socioeconomic interventions combined with research and innovation, though essential, makes the TB portfolio too large for any conventional TB programme to cope with. Implementing the End TB Strategy will therefore require TB programmes to diversify their tracks and change their tactics. TB programmes cannot undertake all the work; it has got to be a combined effort effected through cogent collaborations with multiple partners within and outside the government. For this purpose, TB programme managers will have to transform their roles from being managers implementing the programme to becoming coordinators ably supporting contribution to or implementation of many programme operations to be assumed by relevant ministries, departments, partners, civil society organizations, communities, and other stakeholders. The main intent should be to break all the barriers that people

Panel 1 – The End TB Strategy 2016–2035.

VISION	**A world free of tuberculosis** – zero deaths, disease and suffering due to tuberculosis			
GOAL	**End the global tuberculosis epidemic**			
INDICATORS	**MILESTONES**		**TARGETS**	
	2020	**2025**	**2030**	**2035**
Reduction in number of TB deaths compared with 2015 (%)	**35%**	**75%**	**90%**	**95%**
Reduction in TB incidence rate compared with 2015 (%)	**20%** **(<85/100 000)**	**50%** **(<55/100 000)**	**80%** **(<20/100 000)**	**90%** **(<10/100 000)**
TB-affected families facing catastrophic costs due to TB (%)	**0**	**0**	**0**	**0**

PRINCIPLES

1. *Government stewardship and accountability, with monitoring and evaluation*
2. *Strong coalition with civil society organizations and communities*
3. *Protection and promotion of human rights, ethics and equity*
4. *Adaptation of the strategy and targets at country level, with global collaboration*

PILLARS AND COMPONENTS

1. INTEGRATED, PATIENT-CENTRED CARE AND PREVENTION
- A. Early diagnosis of tuberculosis including universal drug-susceptibility testing, and systematic screening of contacts and high-risk groups
- B. Treatment of all people with tuberculosis including drug-resistant tuberculosis, and patient support
- C. Collaborative tuberculosis/HIV activities, and management of co-morbidities
- D. Preventive treatment of persons at high risk, and vaccination against tuberculosis

2. BOLD POLICIES AND SUPPORTIVE SYSTEMS
- A. Political commitment with adequate resources for tuberculosis care and prevention
- B. Engagement of communities, civil society organizations, and public and private care providers
- C. Universal health coverage policy, and regulatory frameworks for case notification, vital registration, quality and rational use of medicines, and infection control
- D. Social protection, poverty alleviation and actions on other determinants of tuberculosis

3. INTENSIFIED RESEARCH AND INNOVATION
- A. Discovery, development and rapid uptake of new tools, interventions and strategies
- B. Research to optimize implementation and impact, and promote innovations

with TB face in seeking high-quality care while enhancing their experience with the health system and services. Here lies the crucial importance applying the four principles of the End TB Strategy prominently placed above the three pillars. The first and the foremost pillar incorporates the all-important political intervention: government stewardship and accountability.

So, what preparatory steps could TB programmes possibly undertake to make a sound beginning to implementing the new strategy? And how? At a minimum, three logical first steps could be expected from those currently leading national efforts to address the TB epidemic. First, they will need to commence internal, advocacy-oriented consultations with higher officials in the ministry, to initiate timely action and facilitate a smooth transition to the new strategy. For this purpose, preparing material that succinctly summarises current problems and suggests practical solutions could be useful. Secondly, they will need to undertake baseline assessments to define the current status of the various interventions listed under the three pillars of the new strategy. Comprehensive health system and epidemiological assessments should provide insights into overall state of affairs including any need to modify current policies or formulate new ones. They will also help identify the places with poor access to services, and vulnerable populations that need to be prioritized for speedy attention. Baseline assessments should throw light not only on TB-specific interventions such as, for example, the coverage of new diagnostics or the coverage of treatment for drug-resistant TB but also on the general health and social sector initiatives to understand the place of TB in, for example, health-related regulatory frameworks, the national plan for universal health coverage and various available social welfare schemes. And thirdly, they will

need to ask for creation of a high-level coordinating body with the authority and the capacity to oversee the transition to the new strategy, advocate for and help secure resources as well as facilitate intersectoral and inter-stakeholder collaborations. This may be an existing body or a currently working mechanism, or a new one meant for this specific purpose. It should be well-informed not only by representatives of all national stakeholders but also through independent, periodic external evaluations of policies, strategies and programme implementation. Expectedly, setting up of such a high-powered structure spearheaded by a high official in the government should, in itself, announce the arrival of the new strategy, elevate the leadership of national efforts to end TB, and raise the profile of the TB programme. Thus, advocacy, baseline assessments, and a national coordinating mechanism could well be the "abc" of putting the End TB Strategy into practice.

The chiefs of TB programmes and their teams will be well placed to work out how these and other initial steps will likely unfold in their settings. In shaping the first steps, they must equip themselves with a thorough understanding of the WHA resolution and the new strategy – documentary evidence of what their governments have committed – and a good grasp of their own national TB strategic plan with the details of what has been planned and what more needs to be done to achieve a seamless transition to the End TB Strategy.

If focussed internal advocacy leads to taking TB high on the national health agenda, if the baseline assessments feed into modifying the national TB strategic plan bringing it in line with the End TB Strategy, and if a national coordination mechanism backs up the NTP with sound advice, solid support, and secured resources, a country should be all set and ready to kick off as 2016 dawns. Well begun could then turn out to be as good as half done, adding more proof to the proverb.

Disclaimer

The author is a staff member of the World Health Organization. The views expressed here do not necessarily represent the views of the organization.

Conflict of interest

The author has none to declare.

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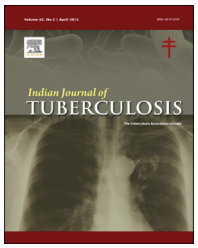

Viewpoint
Is it right time for undergraduate curriculum change based on our National Health Programmes – Tuberculosis Programme a perfect example?

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1. Introduction

TB has existed in India since earliest time, described as Rajayaksma "King of diseases" in Rigveda in 1500 BC. It touches all aspects of human life. India has 21% of global TB burden – the largest number of TB cases in the world. Out of global incidence of 8.6 million cases, Indian share is 2.3 millions.[1] Training and researches done by National TB Institute (NTI) Bangalore, National Institute of Research in Tuberculosis (NIRT), Chennai, National Institute of Tuberculosis and Respiratory Diseases (NITRD), New Delhi along with international agencies (WHO, IUATLD, WORLD BANK) have helped in implementing DOTS and DOTS PLUS, which has gradually reduced the prevalence from 465/lac in 1990 to 230/lac in 2012, in absolute numbers reduced from 40 lacs to 28 lacs annually. Incidence has reduced from 216/lac in 1990 to 176/lac in 2012. Mortality has also reduced from 3.3 lacs to 2.7 lacs annually. Overall success rate of new and retreatment TB cases is 88% and 70% respectively. Training is given to MOs, managers of programme at state/district level and paramedical staff, by these institutions to run the programme successfully.[2] Over the years, we have moved from DOTS strategy to Stop TB Strategy (DOTS PLUS) to Global Strategy and now looking forward to END TB strategy beyond 2015 with an aim to reduce the mortality and incidence of TB by achieving universal health care. The medical education curriculum for undergraduates including internship programme however has not changed appreciably keeping the national needs in mind.

Medical internship training is regulated by Medical Council of India (MCI). Out of one year, two months' training is given in Medicine, two months in Community Medicine, rest eight months in other departments. Only 15 days' elective posting is in TB and Chest diseases.[3] Most of interns, because of PG entrance exams, which follow immediately after internship, are busy in preparations, rather than attending to need of community and patients care. Conditions in govt, as well as private medical institutions are equally bad, as majority of students opt for departments/institutions where work load is less and attendance ensured. Interns posted in PHCs, utilize the opportunity for PGET (post graduate entrance test) preparation and are hardly interested in working for the community service. So the newly passed out medical graduates, are unable to look after National Health Programmes including RNTCP as per the national guidelines. Even during undergraduate teaching, the postings in departments where national programmes are run are done during the time when the students are to appear in university exams of other subjects, leading to absence of students in the concerned subject of national importance.

MCI needs to correct not only the pattern of posting of undergraduates during undergraduate learning but also has to make drastic change in the curriculum of the undergraduates so that competencies and skills are acquired by students to handle National Health Programmes in an effective manner. Tuberculosis and other respiratory diseases which constitute 40% of OPD attendance in our country is the least taught subject in terms of postings during undergraduate teaching and during internship training programme. Tuberculosis and HIV are deadly combination leading to avoidable deaths in productive age group if properly managed by the doctor both

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at individual level and by skillfully running the national control programmes. Number of MDR TB & TB with HIV/AIDS cases are rising. 30% of HIV positive cases have associated TB, 3–5% TB cases are HIV positive. Most of these young, productive people are assets for nation and they are curable. While the high burden of multidrug-resistant tuberculosis (MDR-TB) itself is a matter of great concern, the emergence of extensively drug-resistant TB (XDR-TB) and extremely drug-resistant TB (XXDR-TB) are sources of threat to the community. The proportion of cases with MDR TB was 39.4% during 2005–2007 & 27.8% in 2011–2013, while the proportion XDRTB & XXDR TB got increased from 6.1% & 0% respectively to 10.6% & 5.6% during the same time period. During the same time period, the proportions of cases with Ofloxacin, Moxifloxacin, and Ethionamide resistance significantly increased from 57.6% to 75.3%, from 60.0% to 69.5% and from 24.2% to 52.5% respectively[4] indicating poor management by treating doctors at individual level and under revised national tuberculosis control programme. DOTS strategy, which has been adopted in 148 countries besides India, has high cure rate of 85%, and detection of new sputum smear positive cases rate of 70%. RNTCP is a perfect example of a national programme where doctors, both the govt and private sector along with newer technologies and international agencies are involved to control the disease. Computer training unit is started to support Information and Communication Technology (ICT) Initiatives in the context of the Programme, to support Data Management, Statistical Analysis of research studies, other MIS and to cater to the maintenance of website/upkeep/up-gradation of IT infrastructure of the National TB Institute. Components outlined in the National Strategic Plan for TB control (2012–17) including Case based electronic recording & reporting – Nikshay are important tools for monitoring the programme. An Open Access Repository of abstracts of published scientific papers from all major national institutes has been launched vide URL http://tbresearch.ntiindia.org.in. It attempts to collect, preserve and disseminate the intellectual output of these institutes available in peer-reviewed journals.

2. National institutions and TB control programme

NTI, Bangalore, NIRT, Chennai and NITRD, New Delhi are actively involved in training & research on TB. The aim of RNTCP training programmes at national institutes, is to ensure that programme managers, teachers of medical colleges, medical officers and paramedical staff are equipped with the necessary skills and knowledge required to implement and sustain TB control activities including quality assured diagnosis of TB, management of TB-HIV co-infection, management of drug resistant TB, data management and forging partnerships with all sectors involved in TB control activities. Modular courses for two weeks for State and District level programme Managers, MOs, and faculty from Medical colleges, microbiologists, and three days training' for Laboratory Technicians, Senior Tuberculosis Laboratory Supervisors, besides six days in Line Probe Assays and Liquid Culture for microbiologists & lab technician's collaborative training with SAARC TB and HIV/AIDS Centre, CDC Atlanta, are run. Sensitization of large numbers of medicals/paramedical is a huge challenge. Similarly other National Health Programmes are incorporating the same principles of success and therefore there is a need to club them for training and research purposes.

In view of the above, the training on different aspects of control programme in the country should be seriously undertaken while making curriculum changes in the undergraduate teaching from learning experiences on the lines of Revised national TB control programme. All undergraduates should be given compulsory hands on exposure on different programmes, e.g. under Revised TB Control programme, AFB Staining, identification of *M. Tuberculosis* under binocular microscope, filling and reading of sputum exam forms, categorization of patients for ATT Drugs, TB treatment card filling and monitoring of drugs and all aspects of DOTS & DMC be given. Intern should be made solely responsible for two beds in TB ward, from admission, diagnosis, treatment, to discharge and post-discharge monitoring.

3. Incorporation of "National Health Programmes" in MBBS curriculum as a separate subject

India has presently 30 National Health Programmes running on various diseases & aspects of health. These cover highly problematic communicable & non communicable diseases, concerning many departments i.e. ophthalmic, gynae & obstetrics, pediatrics, oncology and, Psychiatry. It will be prudent to include a subject entirely on "National Health Programmes & National Health Policy", in our MBBS Course, so that students can learn & develop the skills of implementation and monitoring the complex aspects of the control programmes. This will go a long way in prevention, control and elimination of problems due to these 30 diseases, which are affecting major chunk of poor down-trodden populations in India. This will definitely reduce the overall morbidity and mortality burden to a large extent at local, state, and national level.

Conflicts of interest

The author has none to declare.

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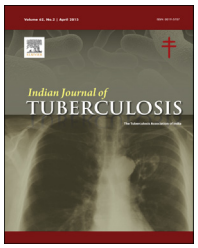

Review Article

Ocular manifestations of tuberculosis

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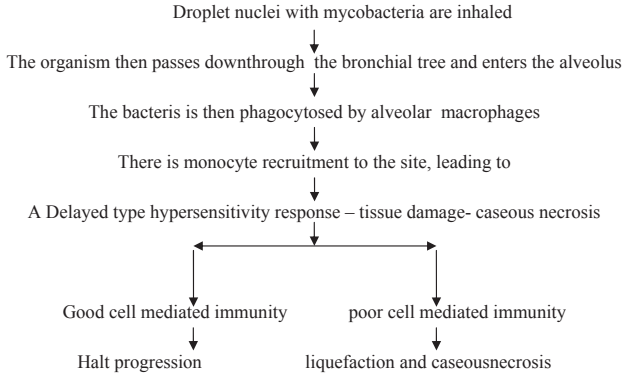
ABSTRACT

Tuberculosis (TB) is a chronic debilitating infection which is caused by *Mycobacteriumn tuberculosis* and other mycobacteria. *Mycobacterium tuberculosis* affects predominantly the lungs although it can affect every organ of the body. Two billion people are affected by tuberculosis. Majority of tuberculosis cases and related deaths occur in Asia.[1] Tuberculosis most commonly occurs in people belonging to the low socio-economic status. Crowding, poor healthcare, unemployment and poor knowledge about basic sanitation increase the risk of acquiring the infection. India is endemic for tuberculosis with 256/lakh population.[2] TB can affect majority of the structures of the eye with marked variability of the lesions. This review will focus on the clinical presentation and management of ocular TB.

The term "ocular tuberculosis" is used to describe infections caused by *Mycobacterium tuberculosis* or any of the three other mycobacteria species (sp. *bovis*, *africanum*, *and microti*) in the eye. The bacteria affects the eye either by a direct invasion after haematogenous dissemination accompanied by local inflammation, or via a hypersensitivity reaction to the bacteria with a focus elsewhere in the body. The factors that increase the risk of acquiring TB are:

- Age (young< 5 yrs and elderly men are at an increased risk).
- Alcoholism and/or drug addiction.
- HIV infection.
- Diabetes mellitus.
- Immunosuppressive conditions.
- Close contact with patients harboring active infection.
- Silicosis
- Poverty and malnutrition.

The pathogenesis of ocular TB involves 5 stages and is summarized below[3–5]:-



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The respiratory tract is the most common portal of entry for infectious droplet nuclei that spread by coughing or sneezing. The bacteria are ingested by alveolar macrophages and multiply within these phagocytes eventually destroying them. The infected macrophages spread by lymphatic flow to the regional lymph nodes and then enter the haematogenous route.

1. Clinical spectrum of intraocular TB

All parts of the eye maybe affected by TB. The most common ocular manifestations are chorioretinitis and uveitis.

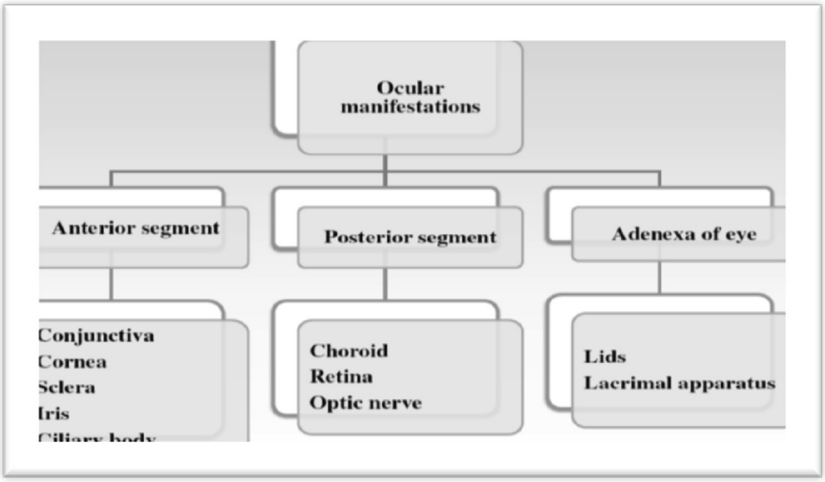


Table classifying the clinical presentations of ocular tuberculosis

2. Tuberculosis of the adnexa

2.1. *Skin of eyelids and peri-orbital area*[6–9]

a) **Lupus vulgaris**—A chronic form of adnexal tuberculosis that affects eyelid skin and occurs in patients who are sensitive to tuberculin antigen. The lesions are solitary, small, reddish brown usually involving the head and neck region and have gelatinous consistency (Apple jelly nodules).
b) **Tubercular lids**—Lesions are popular or indurated nodules or plaque which may ulcerate.
c) **Erythema nodosum**—Reddish nodules on the lids.
d) **Scrofuloderma**—Lesions are firm, painless nodules that overly a tuberculous focus which may break down and suppurate leading to ulcer formation with undermined edges and granulation tissue at the floor. Healing of ulcers is slow and indolent.
e) **Tarsitis**—Inflammation of the tarsal plate of the lids.
f) **Miliary TB of the skin**—Presents as multiple small red papules or macules in cases with fulminant military TB.

2.2. *Orbital tuberculosis-*[10–13]

Orbial TB can occur as ahaematogenous spread or contiguous spread from the neighbouring paranasal sinuses. Manifestations of orbital TB can be grouped under five clinical groups:

- Orbital Periostitis,
- Orbital soft tissue tuberculoma without bony destruction,
- Orbital tuberculoma with bony involvement,
- Orbital spread from paranasal sinuses and dacryoadenitis.

a) **Orbital periostitis**: It affects the people in the first two decades of life as maximum bone growth occurs during these years. It presents as erythema and edema of the lids and conjunctiva with involvement of the spongy vascular tissue of the outer margin of the orbit. It is the most common type of orbital TB and can lead to the formation of a chronically discharging fistula.
b) Tuberculomas of the orbit present as a painless proptosis with or without involvement of bones.
c) Orbital abscesses

2.3. *Lacrimal system*

a) Non specific dacryoadenitis with or without abscess formation is a usual presentation in these cases.
b) Chronic dacryocystitis can present in two forms
   1. Attenuated sclerotic form: It presents as chronic painless hard lobulated mass associated with limitation of extra-ocular movements and ptosis or proptosis.
   2. Active caseous form presenting as red and edematous lesion of lids with fluctuation and fistulization.

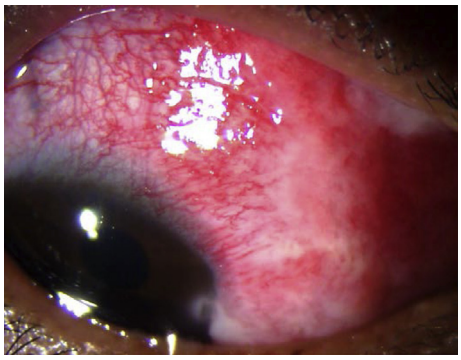


Fig. 1 – Clinical photograph showing conjunctival chemosis and nodule in a patient with active pulmonary TB.

2.4. *Conjunctiva*[14–17]

- Phlyctenulosis is the most common manifestation of tuberculosis which may involve the conjunctiva alone or it may involve the cornea along with conjunctiva near the limbus. Tuberculomas, ulceration and nodules of conjunctiva are very rare. The usual presentation is that of an unilateral conjunctivitis with associated lymphadenitits (Fig. 1).

2.5. *Cornea*

a) Phlyctenular Keratoconjunctvitis: The patients usually present with a gritty sensation and photophobia. The lesions are usually present at the limbus and appear as small pink colored nodules and they may progress centrally accompanied by a leash of superficial vessels. These lesions can ulcerate. The condition is described as a hypersensitivity reaction to the tubercular proteins (Fig. 2).

b) Intersitial keratitis: The Interstitial keratitis presents as peripheral stromal vascularised infiltrate involving superficial and middle layers of the cornea. Attacks are recurrent. It is a hypersensitivity reaction to tubercular proteins (Fig. 3).

2.6. *Sclera and episclera*

Episcleral nodules may form due to a reaction to the mycobacterium protein.

Scleral involvement can be diffuse or nodular. Focal necrotizing anterior scleritis is the most common presentation of tubercular scleritis. Scleral perforation can occur because of necrosis (Fig. 4).

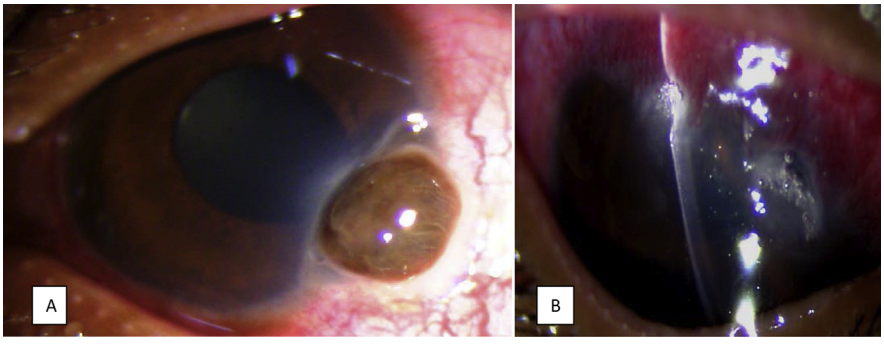


Fig. 2 – (A) Cinical photograph of a patient with sterile perforation with peripheral sclerokeratitis secondary to TB. (B) Superior corneal thinning with phlyctenularkerato conjunctivitis.

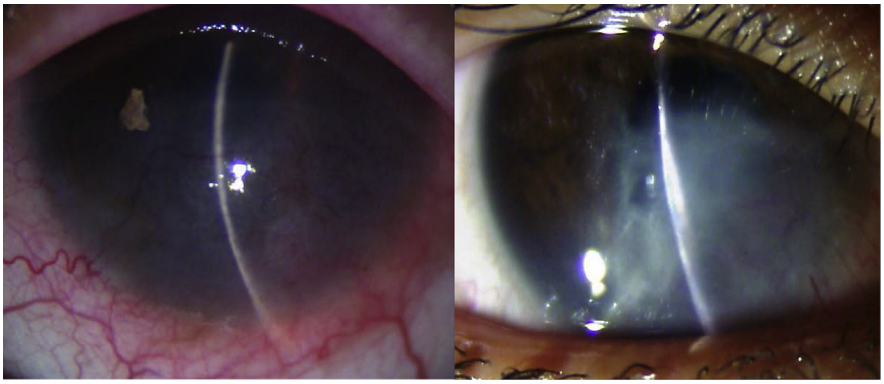


Fig. 3 – Clinical photographs depicting interstitial keratitis in patients with TB.

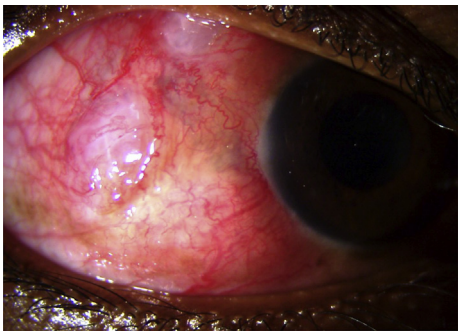


Fig. 4 – Nodular scleritis in a patient with miliary tuberculosis.

2.7. *Uvea*[17–22]

The most common presentation of intraocular tuberculosis in the eye is uveitis. The presentation varies from anterior uveitis to panuveitis.

a) **Anterior uveitis:**

The patients present with a unilateral or bilateral uveitis. It is a chronic, recurrent granulomatous condition and large, mutton fat keratic precipitates are usually present. Iris nodules may be seen. Koeppe's nodules are seen at the papillary border and Bussacas nodules are seen on the iris surface. The uveitis is complicated by the development of cataract, posterior synechiae and maybe accompanied by inflammation in the posterior segment.

b) **Intermediate uveitis:**

Vitreous inflammation presents with moderate to severe cellular reaction in the vitreous cavity, including snowball opacities. The most frequent complications related to TB-uveitis included cystoid macular edema (40%) and cataract (38.9%). Other less common complications were epiretinal membrane, raised intraocular pressure, optic disc pallor, peripheral neovascularization, retinal detachment and vitreous hemorrhage.

c) **Posterior uveitis**—TB can present as posterior uveitis or hypersensitivity retinal vasculitis in the form of Eales disease or primary vasculitis per se. The tuberculous posterior uveitis can present as.
   a) **Choroidal tubercles**—Clinically choroidal tubercle appears as multiple small nodular lesions that may be unilateral or bilateral. They are found mostly in the posterior pole and may have an associated serous retinal detachment. The tubercles can sometimes grow into a single mass lesion called tuberculoma.
   b) **Choroidaltuberculoma**—Choroidal tuberculomas present as a yellowish, subretinal mass and usually have an associated exudative retinal detachment. There may be haemorrhages on the surface of tuberculoma.
   c) **Subretinal abscess**—These lesions are usually seen in patients with disseminated tuberculosis. There is minimal vitreous inflammation. They are yellowish in colour indicating liquefaction necrosis.
   d) **Serpeginous like choroiditis**—It is a chronic recurrent inflammation of the choroids and choriocalliparies. Retina may be involved at later stages. It begins in the peripapillary region and is presumed to be autoimmune in nature. It may be due to an immune mediated hypersensitivity reaction to the bacteria in the or choroid retinal pigment epithelium (Fig. 5).
e) **Retinal vasculitis**—Inflammation of the retinal vessels is a known association of systemic TB, more commonly involving the veins than arteries. Active vasculitis is seen as severe perivascular cuffing, infiltrates, retinal hemorrhages, moderate vitritis, snowball opacities, neuroretinitis and focal choroiditis. Presence of perivascular choroiditis lesions (active or healed) is a strong indicator of tubercular etiology. TB retinal vasculitis may first present with vitreous/preretinal hemorrhage. Tubercular retinal vasculitis and Eales disease are associated with extensive peripheral capillary closure. The presence of associated active or healed patches of focal choroidits along the retinal veins help differentiating TB from Eales disease, sickle cell and Behchets disease(Fig. 6).
f) **Neuroretinitis and optic neuropathy**—The optic nerve may be affected and the manifestations can be in the form of an optic nerve tubercle, papillitis, papilloedema, optic neuritis, retrobulbar neuritis and neuroretinitis.
g) **Endophthalmitis and panophthalmitis**—This form of disease shows rapid progression with destruction of intraocular tissue. When choroidal and subretinal abscesses are left untreated, they undergo liquefaction necrosis with rapid multiplication of acid fast bacilli and can eventually burst into the vitreous cavity, presenting as endophthalmitis or panophthalmitis.

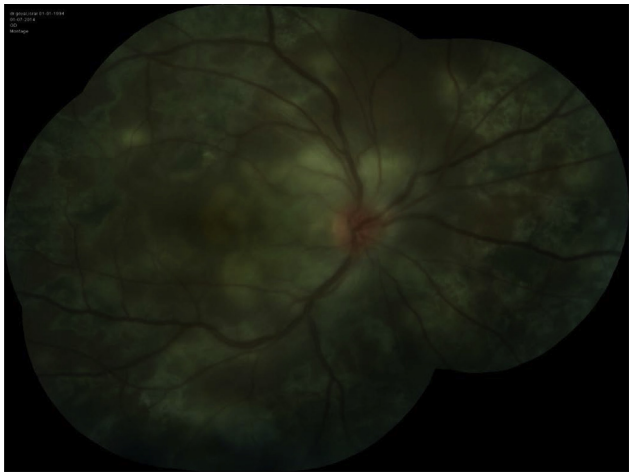


Fig. 5 – Fundus photo of a patient with TB choroiditis.

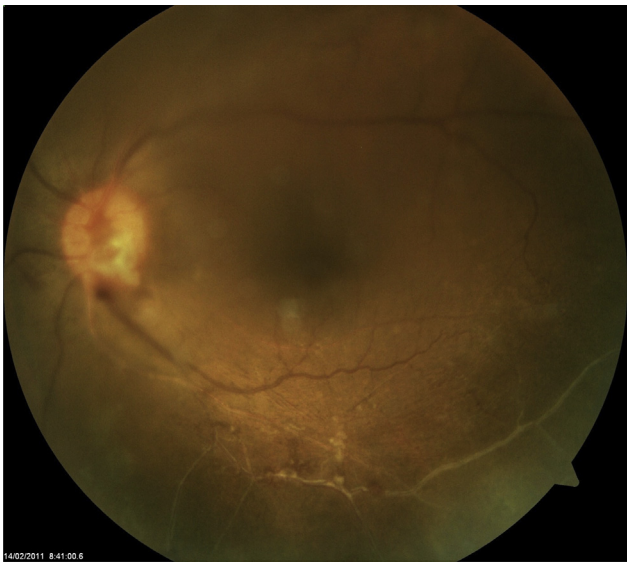


Fig. 6 – Inferior vasculitis with NVD and vitreous haemorrhage in TB vasculitis.

3. Diagnosis and management

There is limited uniformity in the diagnostic criteria for intraocular tuberculosis, and it is also difficult to confirm the diagnosis by laboratory methods.

3.1. *Routine blood investigations*

Routine blood investigations like Complete blood count (CBC) and erythrocyte sedimentation rate (ESR) often may not yield any specific diagnosis, but they should be advised in all patients. Raised white blood cell count is often seen in patients with tuberculosis.

3.2. *Direct investigations*[20,23–25]

a) **Microscopy and culture and sensitivity**—For definitive diagnosis of ocular TB,*Mycobacterium tuberculosis* organism in ocular tissues or fluids should be confirmed either by using histological methods or microbiological investigations. The microscopic identification for acid fast bacilli can be performed on the aqueous or vitreous sample smears using the Zeihl–Neelson or fluorescent staining techniques. Polymerase chain reaction (PCR) technique can be used to demonstrate the antigens in the various ocular tissues. The cultures of *M. tuberculosis* on Lowenstein-Jenson (egg-based LJ) medium are incubated for a minimum of 8 weeks and the colonies are stained and confirmed by Ziehl-Neelson stain.

b) **Biopsy**—Demonstration of granuloma, langerhan's giant cells, acid fast bacilli in biopsy specimen which is generally taken from easily accessible sites like eyelid, conjunctiva, lacrimal glands, and chorioretinal biopsy can be diagnostic.

c) **Polymerase chain reaction (PCR)**—This technique amplifies even very small portion of predetermined target region of *Mycobacterium tuberculosis* complex DNA. It uses a specific automated system which can detect as few as one organism in the fluid such as aqueous or vitreous tap.

3.3. *Ancillary investigations*[20,25–27]

a) **Mantoux skin test**—5 Tuberculin units of purified protein derivative (PPD) is injected intradermally on the volar aspect of the forearm and the diameter of induration is measured (perpendicular to the long axis across the forearm) after 48–72 hrs. An induration of> 10 mm is considered positive especially in patients living in endemic areas or high risk individuals.

b) **Chest radiography**—The chest radiograph provides evidence of active infection and healed/primary or reactivated tubercular lesions. High resolution computerized tomography is considered superior to chest radiography especially in patients in whom systemic TB is suspected.

c) **Interferon gamma release assay (IGRA)**—This test uses specific genomic region present in *Mycobacterium tuberculosis*, ESAT-6 (early secretory antigenic target-6) and CFP-10(Culture filtrate protein –10). These protein stimulate helper T cell which result in secretion of interferon gamma which is measured using an **Enzyme Linked Immunosorbent Assay(ELISA).**

d) **Ocular Imaging: Fluorescein angiography** is commonly used in cases of suspected posterior uveitis due to TB especially to assess choroidal tubercles. Other imaging studies like **ICG angiography, optical coherence tomography (OCT), ultrasonography, and ultrasound biomicroscopy**can also be used. **Indocyanine green angiography helps** in the detection of subclinical choroidal lesions in patients suspected to have intraocular TB. OCT helps to evaluate choroidal neovascular membrane formation and cystoid macular edema. Ultrasonography helps to localize choroidal tubercles especially in cases with hazy media and also to differentiate these lesions from any intraocular malignancy.

4. Medical management[20,28–32]

The treatment of tuberculosis is complex and appropriate management is required to prevent life threatening complications.

Guidelines for diagnosis and management of intraocular Tuberculosis. (Gupta and Gupta)[20]:

5. Intraocular tuberculosis

- One or more of the clinical signs (A) and one of the positive tests (B) could be confirmatory for intraocular TB.

- Any one or more of the clinical signs (A), with any of the positive tests(C), or a positive therapeutic trial (D) should be presumed to have ocular TB

They should get antitubercular therapy provided other causes of infectious uveitis have been ruled out.

A. Clinical signs:
   - Celluar reaction in the anterior chamber/vitreous with or without posterior synechiae.
   - Snowball opacities in the inferior vitreous
   - Perivascular cuffing of inflammatory exudates
   - Solitary or multiple granulomas with/without exudative retinal detachment
   - Subretinal abscess
   - Optic disc granuloma with/without neuroretinitis

B. Ocular investigations:
   - Demonstration of AFB/culture of *M. Tuberculosis* from ocular fluids
   - Positive PCR from the ocular fluids to conserved sequences of *M. Tuberculosis*

C. Systemic investigations:
   - Positive Mantoux reaction
   - Chest radiography suggestive of active/healed TB
   - Evidence of extra-pulmonary TB

D. Therapeutic test
   - A positive response to antitubercular therapy over a period of 4–6 weeks.

Ocular TB is treated as other forms of extrapulmonary TB. The treatment requires a bactericidal drug and a sterilizing agent. The first line anti-tubercular agents are isoniazid, rifampicin, pyrazinamide, streptomycin and ethambutol. The recommended doses for treatment of tuberculosis are:

Drug	Daily dose			
	Children	Adult	Route	Maximum daily dose
Isoniazid	10–20 mg/kg	5 mg/kg	Oral/IM	300 mg
Rifampicin	10–30 mg/kg	10 mg/kg	Oral	600 mg
Pyrazinamide	15–30 mg/kg	15–30 mg/kg	Oral	2 gm
Streptomycin	20–40 mg/kg	15 mg/kg	Intramuscular	1 gm
Ethambutol	15–25 mg/kg	15–25 mg/kg	Oral	2.5 gm

The centre for disease control (CDC) recommends the use of all four drugs (isoniazid, rifampicin, pyrazinamide, andethambutol) for an initial 2-months period followed by a choice of different options over next 4–7months for the treatment of Tuberculosis.

Factors like poor compliance, improper drug regimen, or natural mutations may play a role in the development of drug-resistant tuberculosis. The use of multiple second like agents, with a minimum of three orfour additional antitubercular drugs for 18–24 months is advised in multiple drug resistant tuberculosis (MDR-TB). The additional agents are rifabutin, fluoroquinolones, interferon-g and linezolid.

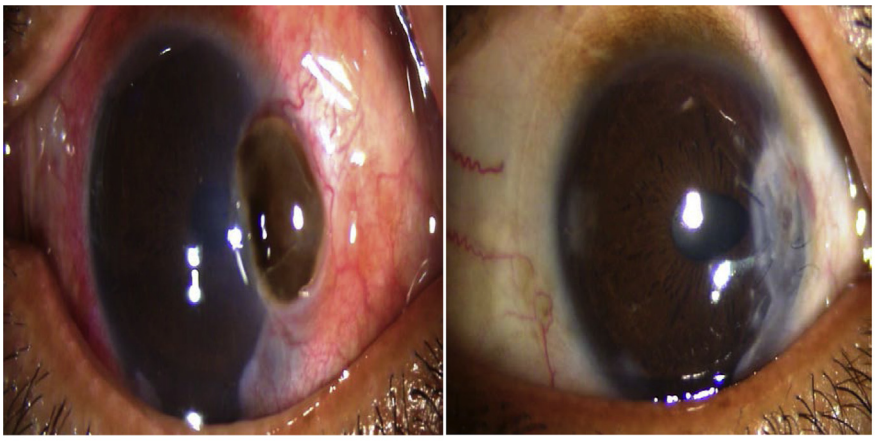
5.1. *Side effect of anti TB drugs*

- Liver function tests and renal functions need to be monitored in patients on ATT.
- Pyrazinamide is hepatotoxic and causes hyperuricemia.
- Rifampin may lead to increase in the clearance of several drugs such as warfarin, corticosteroids, ketoconazole, cyclosporine, oral hypoglycaemic agents and protease inhibitors.
- Rifampin has additive impact on the action of neuromuscular blocking agents.
- Isoniazid is hepatotoxic and can cause a peripheral neuropathy which can be inhibited by the intake of 50 mg of pyridoxine.
- Ethambutol is known to cause optic neuritis, red-green dyschromatopsia, scotomas, disk edema, disk hyperemia, peripapillary splinter haemorrhages, and optic atrophy.

6. Steroids in ocular tuberculosis

- Systemic steroids used for the first few weeks can be used with antitubercular treatment to decrease damage caused to ocular tissues. However, use of steroids alone should be avoided as it can flare up systemic tuberculosis and activate latent lesions.
- Topical steroids are used in the treatment of phlyctenular Keratoconjunctivitis, episcleritis, scleritis, interstitial keratitis and uveitis. Prednisolone acetate eye drops have good anti-inflammatory effect as compared to other preparations. Periocular steroids are indicated in moderate to severe chronic uveitis, posterior scleritis or recalcitrant anterior uveitis.
- There maybe worsening of inflammation following ATT use in patients which may not be controlled with steroids. In such patients immunosuppressants may be added provided HIV and other immunosuppressive conditions are ruled out.

To provide symptomatic relief from pain and formation of posterior synechiae adjuvant medical therapy in the form of cycloplegics and non-steroidal anti-inflammatory drugs should be given.



A PATIENT WITH STERILE PERFORATION SECONDARY TO TUBERCULAR PHLYCETNULAR KERATOCONJUNCTIVITIS SUCCESSFULLY MANAGED WITH A PATCH GRAFT AND INITIATION OF ANTITUBERCUAR THERAPY WITH ADJUVANT STEROIDS

7. Differential diagnosis of ocular tuberculosis

The conditions that can mimic ocular TB are:

Infectious disorders	Non-infectious disorders
Syphilis	Sarcoidosis
Toxoplasmosis	Behcet's disease
Toxocariasis	
Candidiasis	Metastasis
Leprosy	Tumors
Nocardiosis	Autoimmune vaculitis
Leptospirosis	
Lyme disease	
Cat scratch disease	
Coccidiomycosis	

8. HIV and tuberculosis of the eye[33,34]

The association between tuberculosis and HIV infection is attributed to two processes.

- People with latent tuberculosis acquire HIV which can cause reactivation of the tuberculosis
- Patients with HIV infection because of immunosuppression are at increased risk of acquiring active tuberculosis. All parts of the eye can be affected by tuberculosis.
- There can be massive choroidal infiltrates, choroidal nodules, vitritis, endophthalmitis, nonreactive choroidaltuberculoma, choroiditis, multifocal choroiditis, and chorioretinitis.

Tuberculosis has re-emerged as one of the most common causes of mortality. The association of tuberculosis with HIV is also a significant cause morbidity and mortality especially in developing countries. This review highlights the clinical manifestations, laboratory diagnosis, and the current diagnostic criteria that would help in the management of presumed or confirmed ocular tuberculosis.

Conflicts of interest

All authors have none to declare.

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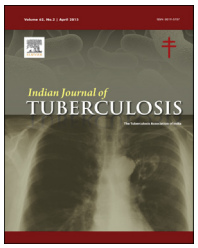

Original Article

A study of adherence to DOTS regimen among pulmonary tuberculosis patients in West Tripura District

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ABSTRACT

Background: Noncompliance to the DOTS regimen leads to treatment failure, relapse, MDR tuberculosis, XDR tuberculosis etc. requiring more prolonged & expensive therapy.
Aim: To assess the adherence rate among pulmonary tuberculosis patients in west Tripura district and to study the factors affecting adherence to DOTS regimen among pulmonary tuberculosis patients.
Material and methods: This community based cross-sectional study was conducted among 220 pulmonary tuberculosis patients registered for treatment with DOTS therapy; under six randomly selected DMC of West Tripura District.
Results: The study revealed that the adherence rate among the pulmonary TB patients was 84.50 percent. Male tuberculosis patients had 87.10 percent less chance of being adherent to the DOTS regimen in reference to females, and Cat I patients were 8.96 times (C.I. 2.689–29.857) more adherent to the therapy compared to the retreatment cases. Again, patients whose continuation phase was supervised as per the guidelines of DOTS were 12.07 times more adherent to the therapy. PTB patients who had the knowledge of supervised therapy in DOTS and curability of the disease, were 4.70 times (C.I. 1.39–15.79) and 9.39 times (C.I. 1.03–85.99) more adherent to the therapy, respectively.
Conclusion: The study showed good adherence to the regimen among pulmonary tuberculosis patients in spite of being a difficult area. It may also help in planning and implementation of tuberculosis control measures by addressing and overcoming the barriers regarding treatment completion.

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1. Introduction

Tuberculosis (TB) remains a world-wide public health problem despite of the fact that the causative organism was discovered more than 100 years ago,[1] and highly effective drugs and vaccines are available since decades making Tuberculosis a preventable and curable disease. As per the WHO Global TB Report 2012, there were an estimated 8.70 million incident cases of TB globally in 2011, out of which, 2.20 million were estimated to have occurred in India.[2]

The treatment of tuberculosis as per RNTCP is through Directly Observed Treatment Short Course (DOTS) chemotherapy which is an internationally recommended strategy to ensure cure by providing the most effective medicine and confirming that it is taken. But poor adherence to the regimen is a major barrier to its global control. Studies conducted in different parts of India showed that 45 to 93 percent of tuberculosis patients are adherent to DOTS therapy.[3–6] Noncompliance to the treatment regimen leads to treatment failure, relapse, MDR tuberculosis, XDR tuberculosis etc. requiring more prolonged & expensive therapy.[7] However, no studies have been conducted in West Tripura District assessing the adherence to DOTS regimen among the PTB patients registered under RNTCP. Hence, the present study was conducted to assess the adherence rate among pulmonary tuberculosis patients in West Tripura district and to study the factors affecting adherence to DOTS regimen among pulmonary tuberculosis patients.

2. Material & methods

This was a Cross-sectional study conducted among Pulmonary TB patients registered under RNTCP in West Tripura District, Tripura. The district has 12 Designated Microscopic Centers (DMC), out of which six DMC was chosen by simple random sampling and the study was conducted among PTB patients registered for treatment, in all the 50 (fifty) DOT centers under the six selected designated microscopic centers. The study was conducted between November 2011 to October 2013.

Considering the adherence rate among pulmonary tuberculosis patients to be 66 percent,[6] an allowance of error of 10 percent of the compliance, and the level of significance (or type 1 error) as 5 percent, the minimum required sample size for assessing the adherence of pulmonary tuberculosis patients to the DOTS regimen was calculated to be 198 using the formulae, $\frac{Z^2_{\alpha/2}pq}{E^2}$.

However, the present study included 220 PTB patients registered within July 2011 to June 2012in the six DMC under RNTCP, by systematic random sampling considering every second patient registered in the tuberculosis register maintained in each DMC.

The study included pulmonary tuberculosis patients who were≥15 years of age and registered for treatment with DOTS therapy at least 3 months before from the date of interview. Those patients who were transferred out or transferred into the DMC area, who did not gave consent for the interview and who could not be traced to their homes in spite of making 2 home visits were excluded from the study.

Data was collected by interviewing the randomly selected pulmonary tuberculosis patients in their home, using a structured, pre-tested, interview schedule and treatment documents of the patients; after taking written informed consent from them.

Data analysis has been done in SPSS version 21 and Epi info version 7.0. Data were expressed in frequency, percentage and statistical analysis has been done using Pearson's chi square test, chi square test with Yates correction, Fisher exact test and multiple logistic regression analysis. P value of <0.05 was considered to be significant.

A patient was said to be adherent if the person takes appropriate drug regimen for required time.[7] A patient was said to be non adherent or non compliant if the tuberculosis patient on DOTS therapy is Missing ≥2 consecutive weeks of DOTS, or there is prolongation of treatment for >30 days due to sporadic missed doses.[8] A patient who has not taken anti-TB drugs for 2 months or more consecutively after starting treatment was said to have defaulted.[9]

The study was sponsored by the Department of Biotechnology and was approved by the institutional ethics committee of Agartala Government Medical College.

3. Results

The present study conducted among 220 pulmonary tuberculosis patients registered under RNTCP revealed that the adherence rate among the PTB patients of the West Tripura District was 84.50 per cent (Fig. 1), i.e., majority of the patients were taking the appropriate drug regimen for the required time.

Among the 15.50 percent noncompliant patients, 13.20 percent patients have either missed ≥ two consecutive weeks of DOTS or had a prolongation of treatment by > 30 days due to sporadic missed doses, but they had not defaulted whereas, 2.30 per cent of the patients defaulted the treatment.

The socio demographic factors which were considered in the present study to affect treatment adherence included age, gender, religion, community, education, occupation and

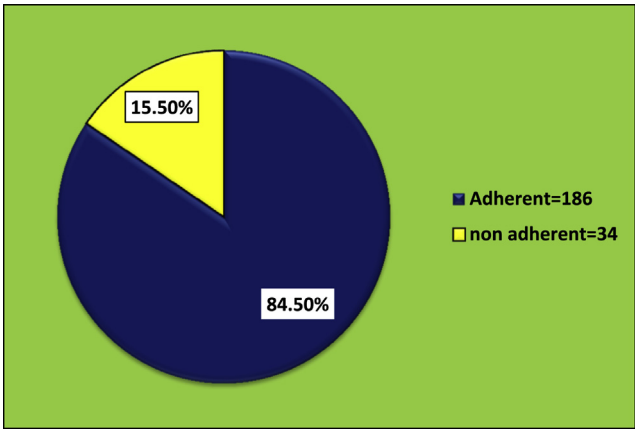

Fig. 1 – Pie chart showing distribution of patients according to their adherence to DOTS therapy.

income of the patients. The study revealed that 91.18 percent of the non adherent patients were male and chi square test with Yates correction showed that there is significant association between the gender of the participants and treatment adherence (P value-0.0464) (Table 1).

The study showed that majority (83.87%) of the compliant patients was under Category 1 treatment and the new cases were significantly more compliant to regimen compared to retreatment cases (p value- 0.000). Beside the study also showed that having no drug ingestion problems significantly increased the treatment adherence (p value-0.000) (Table 2).

Table 3 showed that 41.18 percent of the noncompliant patients were habituated to alcohol consumption and alcohol consumption was significantly higher in the non adherent group (p value-0.002). But tobacco consumption was not found to be associated with treatment adherence.

The study showed that knowledge of the cause of the disease and mode of transmission had no effect on treatment adherence. Majority of the compliant patients (58.10%) had the knowledge regarding the prevention of transmission of disease and it was statistically significant (p value-0.002). The study also showed that majority (97.30%) of the compliant patients had the knowledge that the disease is curable with treatment and they were significantly more adherent to the regimen (p value—0.002). Again, 53.23 percent of the adherent patients had the correct knowledge of the duration of therapy. Beside, patients who had the wrong perception that the disease gets cured with subsidence of symptoms were more on adherence to the regimen (p value- 0.000) and who had the knowledge regarding supervised treatment were significantly more adherent to the regimen (p value- 0.003) (Table 4).

Table 2 – Treatment profile of the patient affecting treatment adherence and non adherence.

	Adherent N = 186, (%)	Non adherent N = 34, (%)	Significance		
			χ^2	df	P Value
Cat 1	156 (83.87)	18 (52.94)	16.629	1	**0.000**
Drug ingestion problems	6 (3.23)	7 (20.59)	15.586	1	**0.000**

Table 3 – Addiction or habituation among patients affecting treatment adherence.

	Adherent N = 186, (%)	Non adherent N = 34, (%)	Significance		
			χ^2	Df	P Value
Smoking tobacco	95 (51.08)	21 (61.76)	1.318	1	0.251
Chewing tobacco	40 (21.51)	8 (23.53)	0.069	1	0.793
Alcohol consumption	33 (17.74)	14 (41.18)	9.397	1	**0.002**

Table 1 – Socio demographic factors for compliant and noncompliant respondents.

		Adherent N = 186, (%)	Non adherent N = 34, (%)	Significance		
				χ^2	df	P Value
Age group (in years)	15–30	61 (32.79)	12 (35.30)	0.343	3	0.952
	31–45	62 (33.33)	12 (35.30)			
	46–60	41 (18.63)	7 (20.58)			
	>60	22 (22.04)	3 (8.82)			
Sex	Male	137 (73.65)	31 (91.18)	4.88[a]	1	**0.027**
Religion	Hindu	173 (93.01)	33 (97.05)		–	
	Muslim	11 (5.91)	1 (2.95)			
	Christian	2 (1.07)	0			
Community	General	85 (45.69)	16 (47.05)	4.621	3	0.202
	ST	34 (18.27)	3 (8.82)			
	SC	45 (24.19)	13 (38.23)			
	OBC	22 (11.82)	2 (5.88)			
Educational status	Illiterate	23 (12.40)	5 (14.70)	2.56	4	0.635
	Sakshar	31 (16.70)	8 (23.50)			
	Primary	79 (42.50)	10 (29.4)			
	Secondary	38 (20.40)	7 (20.60)			
	H/S and above	15 (8.10)	4 (11.8)			
Occupational Status	Unskilled	47 (25.30)	14 (41.20)	7.07	4	0.132
	Skilled	37 (19.90)	7 (20.60)			
	Business	36 (19.40)	6 (17.60)			
	Service/Pension	19 (10.20)	3 (8.80)			
	Household/Housewife/ Unemployed	34 (18.30)	1 (2.90)			
Per capita income per month	<=500	64 (34.40)	17 (50.00)	5.51	5	0.356
	501–1000	57 (30.60)	6 (17.60)			
	1001–1500	24 (12.90)	3 (8.80)			
	1501–2000	17 (9.10)	2 (5.90)			
	2001–2500	8 (4.30)	3 (8.80)			
	>2500	16 (8.60)	3 (8.80)			

[a] = with Yates correction.

Table 4 – Knowledge of pulmonary tuberculosis and DOTS affecting the treatment adherence.

		Adherent N = 186, (%)	Non adherent N = 34, (%)	Significance		
				χ^2	Df	P Value
Knowledge of cause of the disease		28 (15.05)	3 (8.82)	0.479 (with Yates correction)	1	0.488
Knowledge of the mode of transmission		105 (56.50)	13 (38.20)	3.386	1	0.05
Knowledge of prevention of transmission		108 (58.10)	10 (29.40)	9.49	1	**0.002**
Knowledge of symptoms of PTB	*Cough*	158 (84.90)	32 (94.10)	Fisher exact test- P value- 0.2364		
	Fever	94 (50.50)	17 (50.00)	0.003	1	0.954
	Haemoptysis	41 (22.00)	7 (20.60)	0.036	1	0.85
Knowledge of curability		181 (97.30)	28 (82.40)	Fisher exact test- P value-0.002		
Knowledge of duration of treatment		99 (53.23)	17 (50)	0.120	1	0.729
Knowledge that disease does not cure when symptoms subside		83 (44.62)	3 (8.82)	15.47	1	**0.0001**
Knowledge that the drug should be taken under observation		122 (65.59)	13 (38.24)	9.073	1	**0.003**

Table 5 shows that majority of the compliant patients (87.10%) considered the timing of the DOT convenient and it was statistically significant (p value-0.001). Regarding the supervision of therapy, statistical analysis showed that adherence rate was significantly high among those patients whose treatment was supervised during the intensive phase (p value-0.001) and continuation phase (p value- 0.000) of treatment.

Multiple logistic regression analysis considering factors which were found to be significant on bivariate analysis, revealed that females were more adherent to DOTS therapy and males had 87.10 percent less chance of being adherent to the therapy in reference to females. The study also highlighted that the Cat I patients were 8.96 times (C.I. 2.689–29.857) more adherent to the therapy compared to the retreatment cases. Again, patients whose continuation phase was supervised as per the guideline of DOTS were 12.07 times more adherent to the therapy. PTB patients who had the knowledge of supervised therapy in DOTS and curability of the disease, were 4.70 times (C.I. 1.39–15.79) and 9.39 times (C.I. 1.03–85.99) more adherent to the therapy, respectively. Beside, patients who had the knowledge that the disease does not get cured when symptoms subside were 13.31 times more adherent to the regimen. The study also revealed that patients with no drug ingestion problems had 91.10 per cent more chance of being adherent to the DOTS therapy (Table 6).

4. Discussion

The present study has been conducted among 220 pulmonary tuberculosis patients registered under RNTCP in six randomly selected DMC areas of West Tripura District.

The present study showed that majority (84.50%) of the PTB patients in the District were adherent to the DOTS regimen in spite of the fact that it is a difficult area in the North Eastern part of India. The adherence rate of the area was found to be consistent with studies conducted in developed areas of Mumbai (84.00%)[5] and Kerala (88.00%).[3] The adherence rate of the study is also similar to a study conducted in Ethiopia (80.00%).[10] However the adherence rate of the present study is low compared to a study conducted in Nigeria by Bello S.I. et al[11] where 94.60 percent of the patients were adherent to the treatment.

The study revealed that 91.18 percent of the non adherent patients were male and statistical analysis revealed that males were 87.10 percent less adherent to the therapy in reference to females. Similar findings were obtained in a study conducted in Agra by Mittal C et al.[3] Similarly, in a study conducted in Bangalore,[12] males were 2.49 times more non adherent in Category 1 therapy and 2.78 times more non adherent in Category 2 therapy. Thus the present study also revealed that, like other parts of the country male patients are more non adherent to the therapy in this district also. Studies have reported that while men have better access to TB treatment, but the need to earn a livelihood acts as a barrier to completing treatment.[13]

The present study revealed that majority of the compliant patients were new cases of tuberculosis and new cases were 8.96 times (2.69–29.86) more compliant to DOTS therapy compared to retreatment cases. Similar finding has been seen in a study conducted at Agra,[3] and Alexandria.[14] The new pulmonary tuberculosis patients may be more compliant due to comparative short duration of treatment, whereas the long duration of therapy and the recurrence of

Table 5 – Health care system related factors affecting the treatment adherence.

	Adherent N = 186, (%)	Non adherent N = 34, (%)	Significance		
			χ2	df	P Value
Timing of DOT Convenient	162 (87.10)	22 (64.70)	10.530	1	**0.001**
Drugs taken at DOT center	149 (80.11)	27 (79.41)	0.009	1	0.926
Needs transportation cost to the DOT center	56 (30.11)	11 (32.35)	0.068	1	0.794
Supervised treatment in Intensive Phase	162 (87.10)	22 (64.70)	10.530	1	**0.001**
Supervised treatment in Continuation Phase	113 (60.75)	7 (20.59)	18.703	1	**0.000**
Attitude of health worker- Good	186 (100)	34 (100)		–	

Table 6 – Multiple logistic regression analysis showing factors affecting treatment adherence.

		Odds ratio (OR)	95% Confidence Interval for OR	P Value
Sex	Male	0.129	(0.021–0.791)	0.027
	Female	1	.	
Category of treatment	New cases	**8.96**	**(2.689–29.857)**	**0.000**
	Retreatment cases	1	–	
Drug ingestion problems	Present	**0.089**	**(0.015–0.523)**	**0.007**
	Absent	1	–	
Alcohol intake	Present	0.455	(0.132–1.570)	0.213
	Absent	1	–	
Timing of DOT convenient	Yes	3.170	(0.791–12.699)	0.103
	No	1	–	
Treatment under direct Observation in IP	Yes	0.845	(0.225–3.167)	0.803
	No	1	–	
Treatment under direct Observation in CP	Yes	**12.074**	**(2.588–56.333)**	**0.002**
	No	1	–	
Disease gets cured when symptom free and treatment can be stopped	Yes cured when symptom free	0.873	(0.214–3.552)	0.849
	Not cured when symptom free	**13.308**	**(2.599–68.137)**	**0.002**
	Don't know	1	–	
Knowledge that Drug should be taken under observation	Present	**4.699**	**(1.398–15.798)**	**0.012**
	Absent	1	–	
Knowledge of prevention of transmission of the disease by avoiding public coughing.	Present	1.578	(0.511–4.877)	0.428
	Absent	1	–	
Knowledge that disease is curable with treatment	Yes	**9.387**	**(1.025–85.992)**	**0.048**
	No	15.121	(0.622–367.861)	0.095
	Don't know	1	–	

illness may influence the adherence to therapy in retreatment cases.

The present study revealed that the patients who reported drug ingestion problems were 91.10 percent less adherent to DOTS therapy and it was statistically significant (p value-0.007). Similar finding was obtained in studies conducted in South India[4] and Peru[15] where majority of the non adherent patients had drug ingestion problems like difficulty in taking too many pills etc. This shows that drug ingestion problem is a major concern regarding treatment adherence.

Knowledge regarding the disease is an important factor determining the treatment adherence. A study conducted by Vijay S et al[16] showed that patients who had poor knowledge of tuberculosis were 1.88 times more non adherent to DOTS therapy. The present study revealed that patients who had the knowledge that the disease is curable with treatment were 9.38 times (1.02–85.99) more compliant to the treatment compared to those who had no knowledge regarding the curability of the disease. This shows that, having the knowledge that the disease is curable with treatment motivates the patients to improve the treatment adherence.

The study showed that correct knowledge that the treatment cannot be stopped when the symptoms subside increased the treatment adherence by 13.31 times (2.59–68.14). This finding is consistent with a study conducted in Delhi by Ansari et al[17] which showed that 87 percent of noncompliant patients considered that therapy can be stopped if they start feeling better after initiation of treatment. Similar finding was obtained in a study conducted in Raipur.[6] Thus knowledge regarding the importance of completion of the therapy has a major impact on treatment adherence.

Again supervised therapy both during intensive phase and continuation phase according to the guidelines of DOTS, has been found to significantly increase the treatment adherence using Chi square test. But multiple logistic regression analysis showed that when the first dose during Continuation Phase has been supervised it increased the treatment adherence by 12.07 times (2.58–56.33) among the PTB patients. This shows that supervised first dose of the week motivates the patients and imparts the importance of compliance to the regimen even in the continuation phase. Similar studies conducted in China,[18] Malaysia,[19] and Nepal[20] showed that when the treatments were supervised as per the guidelines of DOTS it significantly increased the treatment adherence. Hence it is of great importance to advocate the supervised therapy among the patients to improve treatment outcome.

The present study revealed that the treatment adherence among the pulmonary tuberculosis patients of West Tripura District was good in spite of being a difficult area; with females and Category I patients being more adherent to the DOTS regimen. Beside knowledge of the disease and supervised treatment significantly increased the treatment adherence. But, drug ingestion problems were found to significantly increase the treatment non adherence. Thus, the present study may help in planning and implementation of tuberculosis control measures by overcoming these barriers regarding treatment completion.

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Conflicts of interest

All authors have none to declare.

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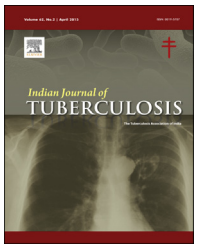

Original Article

Blood levels of isoniazid in Indian children with tuberculosis

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ABSTRACT

Background: Under the Revised National Tuberculosis Control Program (RNTCP) in India children are receiving antituberculosis treatment (ATT) as per a weight band system. In this children may be receiving antituberculosis drugs in doses which may be more or less than that recommended in mg/kg body weight doses. The recommended dose of isoniazid (INH) for intermittent therapy under the RNTCP is 8–12 mg/kg body weight and by the World Health Organization (WHO) for daily therapy is 10–15 mg/kg body weight.

Aims: To evaluate the blood levels and pharmacokinetics of INH, in children suffering from tuberculosis, at doses administered under the weight band system of the Revised National Tuberculosis Control Program (RNTCP) 2009 of India.

Design: Prospective, open label, non-randomized single-dose study conducted in 20 children in the age group 5–12 years attending the outpatient, chest clinic of a tertiary care hospital.

Results: Group I (n = 8) included children who received INH in a dose of 10 mg/kg body weight or more and Group II (n = 12) included those who received INH in a dose less than 10 mg/kg body weight. The mean peak INH concentration (C_{max}) was 6.03 ± 1.4 μg/mL and this was achieved in 2 hours (T_{max}). The mean serum INH concentration was significantly higher in children who received INH in dose more than 10 mg/kg (Group I) as compared to those who received INH in doses lesser than 10 mg/kg body weight (Group II) at all-time points except at 2 hours ($P < 0.05$). The C_{max} was also lower in Group II patients in comparison to Group I patients. Area under the concentration time curve (AUC) was significantly lower in Group II patients (P value 0.002). The elimination half-life of INH was 4.3 ± 0.4 h, elimination rate constant 0.16 ± 0.01/h, the volume of distribution 44.05 ± 5.3 L and clearance 7.1 ± 0.8 L/h.

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Conclusions: Lower blood levels and AUC of INH were achieved in children receiving doses of INH lesser than 10 mg/kg body weight. Long elimination half-life of INH is indicative of a slower rate of metabolism. Lower INH levels despite a slower rate of drug metabolism indicate caution with the INH doses being administered to children for intermittent therapy under the RNTCP.

1. Introduction

Under the Revised National TB Control Program (RNTCP) in India, children are administered thrice weekly doses of antituberculosis drugs according to a weight band system.[1] Under RNTCP 2009, INH was being administered at a dose of 10 mg/kg body weight (8–12 mg/kg) thrice weekly to both adults and children. Recently the RNTCP has been revised and INH dose has been specified as 10 mg/kg body weight to a maximum of 300 mg for intermittently (thrice weekly) therapy.[2] The World Health Organization (WHO) has recommended INH in an oral dose of 10–15 mg/kg body weight in children, to be administered daily.[3] The WHO has also recommended that in countries with a high prevalence of HIV, antituberculosis treatment should not be given intermittently to children.[4]

In India under the RNTCP INH has been administered in a dose range lesser than that recommended by WHO, intermittently to children. India also has a high prevalence of HIV infection. Under the weight band system of RNTCP 2009, some children were getting doses lesser than 10 mg/kg body weight of INH, a dose which is at the lower end of the dose range recommended by the WHO for daily therapy and the average dose according to RNTCP guidelines for intermittent therapy. The basis of intermittent therapy is that appropriate peak drug levels be achieved, which will inhibit mycobacterial growth sufficiently till the administration of the next dose of the drug. Low doses of antituberculosis drugs administered intermittently may result in inadequate drug concentrations in the body. This may contribute to treatment failure, relapse and drug resistance.

There is lack of sufficient data in Indian pediatric patients on the blood levels of INH achieved with the weight band system of RNTCP 2009. This study was conducted to observe the blood levels of INH achieved in children falling under Weight band 2 and 3 of RNTCP.

2. Methods

An open-label, prospective, non-randomized single dose study was conducted in newly diagnosed children suffering from tuberculosis attending the chest clinic of Lok Nayak Hospital, New Delhi, India. The study was conducted between 2011 and 2012, prior to the official announcement of the change in guidelines for pediatric tuberculosis in 2013. The study was approved by the Institutional Ethics Committee. Written informed consent was obtained from parents or guardians of all the children and written informed assent was obtained from all the subjects above 7 years of age.

2.1. Subjects

A total of twenty children in the age group of 5–12 years, newly diagnosed with pulmonary or lymph node tuberculosis, were enrolled in the study. Diagnosis of tuberculosis was based on relevant clinical history, physical examination, chest X-ray, Mantoux test and fine needle aspiration cytology of accessible lymph nodes, wherever required. Patients with hematological, hepatic and renal functions within normal range were included. Children with severe tuberculosis requiring hospital admission, presence of any other diseases and having history of any concomitant or long term drug intake were excluded from the study.

2.2. Study design

Patients fulfilling the inclusion criteria were admitted one day prior to study commencement in the Paediatric ward of Lok Nayak Hospital. After overnight fasting, a single dose of INH was administered at 6.00 am. Children with body weight between 11 and 17 kg (Weight Band 2) were given a single oral INH tablet 150 mg and those with body weight between 18 and less than 25 (Weight Band 3) were administered single oral dose of INH 225 mg. These doses were administered as per RNTCP 2009 guidelines for intermittent therapy of tuberculosis in children. A standard breakfast and lunch was administered 2 and 6 h after INH administration, respectively. Regular antituberculosis treatment began 24 h later.

2.3. Sample collection

Venous blood samples (1.5 mL) were collected at 0, 1, 2, 4, 6, 10 and 24 h. Serum was separated within 1 h, deproteinized within 4 h and stored at −20 °C till isoniazid estimation.

2.4. Assay method

Estimation of isoniazid was done by the microspectrofluoro metric method of Miceli et al.[5]

The INH dose administered to individual patients was converted to mg/kg dose and the patients were divided into two groups. Group I consisted of those patients who received INH in a dose of 10 of mg/kg or more and Group II who received INH in a dose lesser than 10 mg/kg. Comparison of serum INH concentrations over different time points, and pharmacokinetic parameters, peak serum concentration (C_{max}), time to achieve the peak concentration (T_{max}), area under the serum concentration vs time curve from zero to twenty four hours and zero to infinity ($AUC_{(0-24)}$, and $AUC_{(0-\infty)}$), elimination half-

life ($t_{1/2}$), elimination rate constant (K_{el}), volume of distribution (V_d) and clearance (CL)was done between the two groups.

2.5. *Pharmacokinetic analysis*

A single open compartment model was used to calculate the pharmacokinetic parameters of INH using WinNonlin Professional Version 4.0 (Pharsight Corp, Mountain View, CA, USA). The demographic characteristics, baseline investigations, serum INH concentrations and pharmacokinetic parameters between Group I and Group II were compared using Student's t-test for unpaired data. For statistical analysis P value of <0.05 was considered significant at a confidence interval of 95%. The results are expressed as mean ± standard error of mean.

3. Results

All 20 patients completed the study. In both groups, patients were comparable in their demographic profile (Table 1). Two patients were in weight band 2 and eighteen patients were in weight band 3. When calculated in mg/kg body weight doses, it was observed that twelve out of twenty patients received INH in a dose less than 10 mg/kg body weight. The mean dose of INH administered was 10.49 ±0.13 mg/kg body weight (10.22–11.25 mg/kg) in Group I and 9.39 ± 0.1 mg/kg body weight (8.9–9.95 mg/kg) in Group II.

The mean serum concentration of INH at 1 h was 4.03 ± 0.12 μg/mL, it rose to 6.31 ± 0.13 μg/mL at 2 h, at 4 h the INH levels started declining to 3.66 ± 0.11 μg/mL, at 6 h the mean serum INH concentration was below 2 μg/mL and then gradually decreased to 0.15 ± 0.01 μg/mL over 24 h in all 20 patients (Fig. 1). The INH concentrations were lower in Group II as compared to Group I up to 24 h at all-time points (Fig. 2). This difference was significant at all-time points except at 2 h (Table 2). The peak concentration of isoniazid was obtained at 2 h in all 20 patients. The mean C_{max}, AUC_{0-24} and $AUC_{(0-\infty)}$ was less in Group II in comparison to Group I (Table 3). The elimination half-life was 4.3 ± 0.6 h (3.93–4.59 h). The other pharmacokinetic parameters are shown in Table 3.

Table 1 – Demographic characteristics and baseline investigations (mean ± SEM) in Group I (children who received INH in a dose of 10 mg/kg body weight or more) and Group II patients (who received INH in a dose less than 10 mg/kg body weight).

Patient characteristic	Group I (n = 8)	Group II (n = 12)	Normal range
Age (years)	8.8 ± 0.4	10.75 ± 0.3	–
Sex (Male:Female)	0:8	1:11	–
Weight (kilograms)	21.45 ± 0.3	22.59 ± 0.7	–
Height (centimeter)	122.2 ± 1.2	123.5 ± 0.9	–
MAC (centimeter)	12.03 ± 0.3	12.1 ± 0.13	–
Hemoglobin (gram %)	11.7 ± 0.4	11.49 ± 0.22	11–18
TLC ($\times 10^3/mm^3$)	6.97 ± 0.2	6.5 ± 0.19	4–11
ESR (mm/h)	16.75 ± 2.3	19.25 ± 1.5	0–20
Serum bilirubin (mg %)	0.7 ± 0.03	0.6 ± 0.03	0.5–1.2
SGOT (IU/L)	19.12 ± 0.69	21.16 ± 0.62	10–40
SGPT (IU/L)	20.75 ± 1.37	20.91 ± 0.69	10–40
S. ALP (KA^0)	15.32 ± 1.06	16.48 ± 1.03	3–20
Total Protein (g %)	6.32 ± 0.08	6.42 ± 0.11	6–8
Serum Albumin (g %)	4.06 ± 0.14	4.16 ± 0.05	3.5–5.5
Serum Globulin (g %)	2.11 ± 0.03	2.22 ± 0.1	2–3.5
Blood Urea (mg %)	24.25 ± 0.6	24.66 ± 0.4	15–30
Serum creatinine (mg %)	0.72 ± 0.06	0.72 ± 0.03	<1.4

SEM: Standard Error of Mean, MAC: Mid arm circumference, TLC: Total leucocyte count, ESR: Erythrocyte sedimentation rate, SGOT: Serum glutamate oxaloacetate transaminase, SGPT: Serum glutamate pyruvate transaminase, S.ALP: Serum alkaline phosphate.

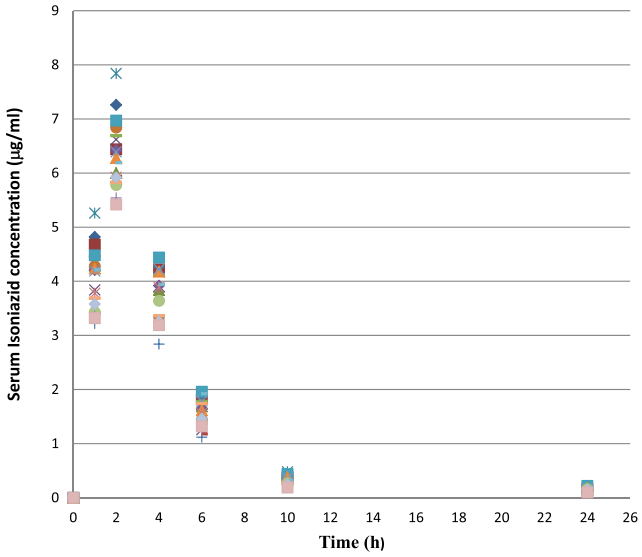

Fig. 1 – Isoniazid concentrations (μg/ml) at different time intervals after drug administration.

4. Discussion

Recently there has been increasing awareness that doses of antituberculosis drugs in children require reconsideration as they are mostly based on pharmacokinetic studies done in adults. It has been observed that drug pharmacokinetics and

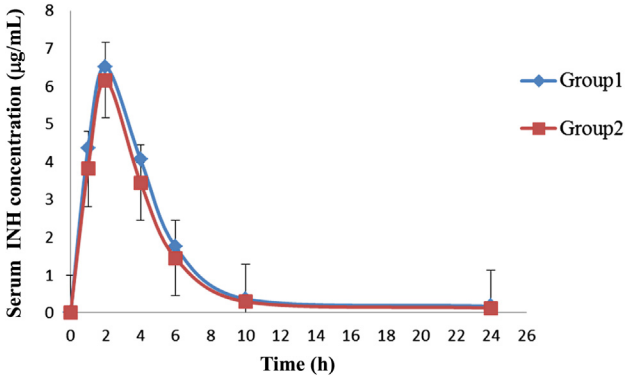

Fig. 2 – Serum concentration time curve of INH over 24 h in patients in Group I (n = 8) and Group II (n = 12) [Each point represents Mean ± SEM].

Table 2 – Comparison of serum isoniazid concentrations in μg/mL (Mean ± SEM) over 24 h in patients of Group I and Group II.

Time (h)	Serum INH concentration) (μg/mL)		
	Group I	Group II	P Value
0 h	00	00	00
1 h	4.36 ± 0.07	3.82 ± 0.17	0.03
2 h	6.52 ± 0.14	6.16 ± 0.19	0.12
4 h	4.06 ± 0.08	3.45 ± 0.12	0.002
6 h	1.75 ± 0.04	1.45 ± 0.07	0.005
10 h	0.37 ± 0.01	0.30 ± 0.02	0.021
24 h	0.18 ± 0.01	0.13 ± 007	0.003

pharmacodynamics in children may be different in comparison to adults.[6–9]

INH is a major component of all antituberculosis regimens. Studies in adults have demonstrated dose related efficacy of INH with regard to early bactericidal activity and long term clinical outcomes.[10–13] The dose of INH would thus be a critical determinant in the overall efficacy of antituberculosis drugs. The dose of INH would also be higher when the drug is administered intermittently.[11,14]

In this study the blood levels of INH achieved in children in weight band 2 and 3 were analyzed. A dose of 10 mg/kg body weight of INH was selected for dividing the children into two groups, Groups I and II. This was done as 10 mg/kg is the lowest dose in the recommended dose range of 10–15 mg/kg body weight/day by WHO. The concentrations of INH attained in the serum at all-time points and the AUC was lower in the Group which received INH in doses lesser than 10 mg/kg body weight. The difference between the peak INH concentrations achieved in both the groups is not much because most of the patients were from weight band 3 and their individual weights were comparable. Thus they were getting relatively the same amount of INH in mg per kg body weight (8.9–11.2 mg/kg body weight). The elimination half-life was long indicating a slower rate of drug metabolism. Studies have shown that majority of Indian children have slow acetylator status.[15] The volume of distribution and clearance was comparable to previously reported studies.[16,17] The differences in $t_{1/2}$, K_{el}, and CL between the two groups in addition to the lower INH dose received may be contributing to the lower INH blood levels in Group II.

The proposed optimal maximum serum INH concentration for anti-mycobacterial action in adults with a 300 mg daily dose is stated to be 3–5 μg/mL.[18] After a dose of INH 900 mg in adults, a peak level of 9–15 μg/mL has been recommended in biweekly therapy.[18] There are no data available on the optimal serum INH concentration in children for daily and intermittent (thrice weekly) therapy. In this study the peak INH levels achieved in both the groups was 6.53 ± 0.15 and 6.13 ± 0.19 μg/mL at 2 h. By six hours INH levels had declined below 2 μg/mL in all patients (Fig. 1). In absence of recommended INH levels for thrice weekly therapy it is difficult to definitely comment but based on the above stated optimum levels it appears that these levels may be low for thrice weekly intermittent therapy where the efficacy of the drug is based on adequate peak drug levels being achieved at regular intervals. This, together with the fact that all children in this study had long elimination half-lives implies that determining the optimum INH dose in Indian children will require greater correlation between pharmacokinetic and pharmacodynamic outcomes. A positive correlation between the C_{max} of antituberculosis drugs and disease outcome has been seen. It has been observed that INH concentrations were significantly lower in children with unfavorable outcomes than in those with favorable outcomes.[19]

Various studies have shown that lower INH levels are achieved in children compared to adults with the same mg/kg dose.[20,21] Younger children eliminate INH faster than older children and as a group faster than adults. They thus require a higher mg/kg body weight INH dose to achieve serum concentrations comparable to adults. Children have higher hepatic metabolic capacity than in adults, because of larger liver mass relative to whole bodyweight in children. Younger children have a larger volume of distribution of INH in comparison to older children and adults. Even amongst children INH levels were much lower in younger children and in fast acetylators.[19,22] Again INH distributes in a compartment comparable to total body water. During growth, the proportion of total body water to bodyweight changes from 70% at birth to 50% in adulthood.[23–25] It has been suggested that INH doses should be individualized based on age, acetylator status and disease in children.[19,26]

In a recent study low serum concentrations of isoniazid, rifampicin and pyrazinamide in children younger than 2 years

Table 3 – Comparison of Pharmacokinetic parameters of patients in Group I and Group II. (Group I – patients receiving INH in a dose ≥10 mg/kg body weight and Group II – patient's receiving INH in a dose ≤10 mg/kg body weight), values are in Mean ± SEM.

Pharmacokinetic parameter	Group I	Group II	95% CI of difference between mean	P Value
C_{max} (μg/ml)	6.53 ± 0.15	6.13 ± 0.19	−0.15, 0.95	0.12
T_{max} (h)	2	2	–	–
AUC_{0-24} (μg h/ml)	32.18 ± 0.57	28.01 ± 1.04	1.3, 7.04	0.002
$AUC_{0-\infty}$(μg h/ml)	32.32 ± 0.64	28.84 ± 1.07	0.51, 6.45	0.002
$t_{½}$ (h)	4.38 ± 0.055	4.189 ± 0.05	0.01, 0.4	0.023
K_{el} (h^{-1})	0.16 ± 0.002	0.17 ± 0.002	−0.02, 0	0.021
V_d (L)	42.76 ± 0.49	44.90 ± 2.003	−7.3, 3.1	0.321
CL (L/h)	6.77 ± 0.126	7.40 ± 0.275	−1.42, 0.02	0.05

SEM: Standard error of the mean, C_{max}: Peak serum concentration attained, T_{max}: Time to reach peak serum concentration, AUC_{0-24}: Area under serum concentration time curve over 24 h, $AUC_{0-\infty}$: Area under serum concentration time curve over infinity, $t_{½}$: Elimination half-life, K_{el}: Elimination rate constant, V_d: Volume of distribution, CL: Clearance.

of age were documented, following the previous WHO dose recommendations. In contrast, administration of the revised WHO recommended dose (10–15 mg/kg body weight) resulted in satisfactory serum drug concentrations above therapeutic concentration.[27] Based on observations that lower blood levels of INH are achieved in children in comparison to adults at the same mg/kg dose, authorities all over the world have revised their dose recommendations for antituberculosis drugs. The American Academy of Paediatrics recommends 10–15 mg/kg/day dose of INH in children for daily therapy. Other National Programmes such as those in Japan, Mexico and Philippines also now recommend INH in a dose of 10–15 mg/kg/day for children.[28]

The Government of India has recently revised the National Guidelines on diagnosis and treatment of Pediatric tuberculosis.[2] In these, the dose of INH has been changed to 10 mg/kg and the number of weight bands have also been increased to six.[2] This will result in INH being delivered in a dose ranging from 10 to 13 mg/kg in different weight bands. However the drug will be given intermittently. Whether these changes will result in optimum therapeutic drug levels when administered intermittently is not known. As in this study we observed that even with 10 mg/kg or more doses and a prolonged half-life of INH, there is a probability that the peak levels achieved may not be adequate for intermittent therapy. The INH levels are further dependant on the age of the child and acetylator status with younger children and fast acetylators showing lower drug levels at the same mg/kg body weight dose.

Limitations of the study: i) Sample size – The sample size of the study was small. This is because pharmacokinetic studies involving repeated blood sampling raises ethical issues. ii) Age group – The age group of subjects included was 5–12 years. This was done to maintain homogeneity of pharmacokinetic data as many changes in metabolic capacity and maturation of enzymes occur in children in the initial years. iii) The clinical outcome of treatment was not assessed. This was because the study had to be completed in a specific duration of time and follow up of all patients till end of therapy was not possible. iv) Lack of available data on therapeutic levels for INH in children receiving thrice weekly therapy.

Under the weight band system of RNTCP 2009, children were receiving INH in doses lesser than 10 mg/kg which resulted in lower INH levels. The formulation of weight bands under RNTCP 2013 guidelines may ensure delivery INH in doses of 10 mg/kg or more. In view of the fact that the drugs are being given intermittently, pharmacokinetic and clinical outcome studies needs to be done in children to better define the appropriate dose in the concerned population.

Contributors

GMR was involved in preparing the study protocol, sample collection, biochemical analysis, calculation of results and preparing manuscript. He will act as a guarantor of the study. VR conceived and designed the study. She was involved in supervision of the study and analysis and interpretation of results and preparation of the manuscript. GRS and AK contributed to planning of the study and management of pediatric tuberculosis patients. TKM supervised the biochemical analysis. All the authors contributed to the preparation of manuscript and the final manuscript was approved by all authors.

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Conflicts of interest

All authors have none to declare.

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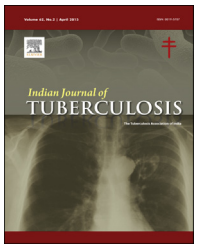

Original Article

Rapid identification of *Mycobacterium tuberculosis* complex in clinical isolates by combining presumptive cord formation and MPT64 Antigen Immunochromatographic Assay

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ABSTRACT

Purpose: Combining the results of presumptive cord formation in smear and MPT64 Antigen Immunochromatographic Assay has been suggested to reduce the false negative and positive rates for identification of *Mycobacterium tuberculosis* (MTB) complex in liquid culture. This study was done to evaluate the clinical utility of combining the results of the two tests for rapid identification MTB complex in mycobacterial isolates.

Methods: 484 isolates of mycobacteria obtained in MGIT culture were identified using presumptive cord formation in smear and further by MPT64 Antigen ICT assay. Result obtained were analyzed taking PNB inhibition test as the reference standard.

Results: Combining the results of the two tests, 464 (95.9%) isolates were correctly identified while discrepant results were obtained in 20 (4.1%) isolates. When the results of the two tests were intersected, the specificity and PPV was 100%, but the sensitivity decreased to 96.4% and the NPV to 68.6%. On the other hand, when the results of the two methods were combined, the sensitivity and NPV was 100%, but the specificity decreased to 88.6% and the PPV to 99.1%.

Conclusion: Presumptive cord formation and MPT64 antigen ICT assay can be used in combination for identification of MTB complex. When both the test are positive, the culture can be reported to contain MTB complex. If both the tests are negative, the culture should be reported to contain NTM. Only when discrepant results are obtained by the two tests, further evaluation is necessary to ensure an accurate diagnosis.

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1. Introduction

The global burden of tuberculosis (TB) remains enormous. In 2012, there were an estimated 8.6 million estimated cases of TB, out of which 2.3 million were from India. The emergence and spread of drug-resistant *Mycobacterium tuberculosis* (MTB) strains poses significant challenges to disease control. As per the WHO Global Report on Tuberculosis 2013, India accounts for 64,000 multidrug-resistant tuberculosis (MDR-TB) cases out of 300,000 cases estimated globally to occur among the notified pulmonary TB cases annually.[1] Rapid and accurate diagnosis of these cases is crucial for patient management and control of disease transmission.

Culture remains the gold standard for the definitive diagnosis of tuberculosis. Introduction of liquid culture technology have aided in the rapid isolation of mycobacterial species. Various commercially available liquid culture systems use Middlebrook 7H9 broth for better recovery and faster growth of mycobacteria. The media is very sensitive and as a result is prone to contamination not only by non mycobacterial organisms but also by Non tuberculous Mycobacteria (NTM) originating from patients flora or laboratory reagents. These NTM isolates have to be differentiated from MTB complex before proceeding to drug susceptibility testing as clinical significance of NTM, especially in high prevalence TB setting is still under debate.[2]

Several methods are available to identify MTB and differentiate it from NTM. Molecular methods and high performance liquid chromatography have been described as accurate and rapid, but require procedures that are technically complex, laborious and costly. Para-Nitrobenzoic Acid (PNB) inhibition test is recommended for differentiation of MTB from NTM in commercial liquid culture systems but it requires additional time of 4–11 days from the detection of a positive culture to the identification of an isolate.[3]

Presumptive identification of MTB complex by its ability to grow as serpentine cords in liquid culture medium has been previously reported.[4,5] Visualisation of cord formation by Ziehl–Neelsen (ZN) stain provides rapid preliminary information before the results of other identification methods are available. However few NTMs also form true cords or pseudocords, that are loose aggregate of bacilli, in liquid media leading to false results.[5] MPT64, a 24 kDa protein, is one of the major antigens secreted by members of MTB complex in culture medium. Detection of antigen by immunochromatography (ICT) using monoclonal antibodies against MPT64 antigen has been suggested to be a rapid and cost effective method of identification of MTB complex isolates.[6] The specificity and sensitivity of >92% has been reported in various studies.[6–8] Reported false-negatives have likely resulted from low numbers of bacteria in the cultures or mutations in the MPT64 gene of the bacteria.[7,9]

This study was undertaken to evaluate the clinical utility of combining presumptive cord formation and MPT64 Antigen ICT Assay to rapidly and accurately identify MTB complex in positive liquid culture isolates.

2. Methods

This prospective study was conducted at a large tertiary care hospital of India. Specimens submitted for routine analysis in mycobacteriology laboratory were studied. All procedures requiring biosafety precautions including processing of specimens, inoculation of media, and identification were performed in a Class II Biosafety Cabinets dedicated for mycobacterial work.

A total of 484 mycobacterial isolates obtained in Mycobacterium Growth Indicator Tube (MGIT) liquid culture (Becton Dickinson and Company, USA) from 2286 consecutive clinical specimens over a period of one year were included in the study. Smears made from positive MGIT tube were stained with ZN stain to confirm the isolate as Acid Fast Bacilli (AFB) and serpentine cord morphology was recorded. Serpentine cording was defined as tight, rope-like aggregates of acid-fast bacilli in which the long axes of the bacteria paralleled the long axis of the cord. Microscopic morphology and organism orientation that did not meet the above criteria were considered negative for cording (Fig. 1).

All AFB positive isolates were further subjected to identification of MTB complex by MPT64 Antigen ICT assay (SD Bioline TB Ag MPT64 rapid kit) as per manufacturer's instructions. Briefly 100 μl of sample obtained from positive MGIT tube was applied directly to the sample well without preparation. Tests were interpreted 15 min after sample application. The presence of a control band alone indicates a negative result, whereas the presence of two color bands (control and test bands), no matter which band appears first, indicates a positive result for MTB complex. A color band of any intensity was read as a positive reaction. The absence of control band after the test was considered invalid (Fig. 2).

Identification of MTB complex by PNB inhibition test was taken as reference standard. PNB was added to get a final concentration of 500 μg/ml in the MGIT tube. 0.5 ml of positive culture was inoculated into two MGIT tubes with and without PNB and incubated at 37 °C. MGIT tubes were read daily using Micro MGIT fluorescence reader (Becton Dickinson and Company, USA). A strain was considered susceptible when the tube containing the PNB did not show fluorescence 2 days after positive results were observed in the control tube, whereas if fluorescence occurred the strain was considered resistant. Discordant results were resolved by means of results of biochemical tests and molecular test – Line probe assay. The result obtained were subjected to statistical analysis.

The reference strain H37Rv was used as positive control for MGIT, MPT64 antigen ICT assay and PNB inhibition test.

3. Results

Of the 484 mycobacterial isolates obtained in MGIT liquid culture, 449 were identified as MTB complex and 35 as NTM. Result of identification by presumptive cord formation and MPT64 Antigen ICT assay in comparison to reference PNB inhibition test is shown in Table 1. Four hundred and thirty eight MTB complex isolates and three NTM isolates demonstrated

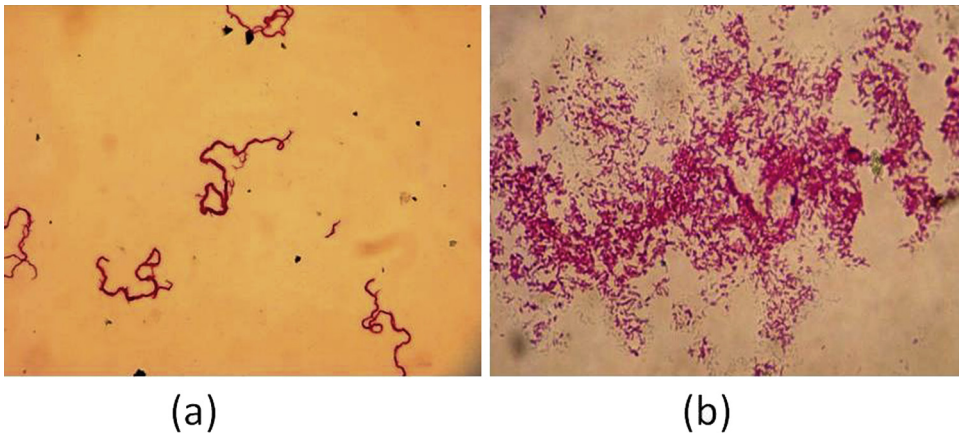

Fig. 1 – Differentiation of (a) *Mycobacterium tuberculosis* complex and (b) Non Tuberculous mycobacteria (NTM) in culture positive MGIT by presumptive cord formation by ZN stain (40×).

serpentine cording in cultured smears. No cording was noted in 11 isolates which were finally identified as MTB complex. MPT64 antigen ICT assay performed on 484 AFB smear positive culture isolates correctly identified 444 of MTB complex isolates and 34 of NTM isolates. Five NTM isolates and one MTB complex isolate was misidentified by MPT64 antigen ICT assay.

To reduce the false negative and positive rates results of the two tests were combined for MTB complex identification. Table 2 shows combined results of presumptive cord formation and MPT64 Antigen ICT assay in culture positive MGIT tubes. Combining the two tests 464 (95.9%) isolates were correctly identified while discrepant results were obtained in 20 (4.1%) isolates. On further evaluation by molecular tests 16 of these isolates were confirmed to be MTB complex while 4 isolates were identified as NTM. Comparison of results for identification of MTB complex by presumptive cord formation in smear, MPT64 Antigen ICT assay and intersection and union results obtained after combining the two tests is shown in Table 3. When the results of the two tests were intersected, the specificity and PPV was 100%, but the sensitivity decreased to 96.4% and the NPV to 68.6%. On the other hand, when the results of the two methods were combined, the sensitivity and NPV was 100%, but the specificity decreased to 88.6% and the PPV to 99.1%

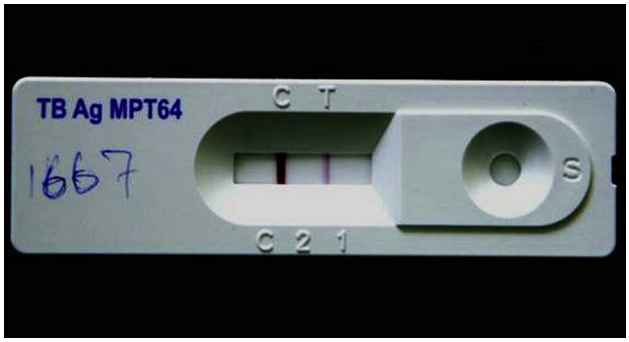

Fig. 2 – MPT64 Antigen ICT assay.

4. Discussion

Rapid and accurate bacteriological diagnosis of tuberculosis plays a key role in management of the disease. Because of its high sensitivity and specificity culture is the current gold standard for diagnosis of tuberculosis. Although most culture-positive mycobacteria are *M. tuberculosis* in regions where tuberculosis is highly prevalent, NTM isolates have been increasing gradually. The isolation rate of NTM from India has been reported ranging from 0.5% to 8.6%.[10] In our study 7.23% of isolates obtained on MGIT liquid culture were identified as

Table 1 – Identification of MTB complex by Presumptive cord formation and MPT64 Antigen ICT assay in comparison to reference PNB inhibition test.

PNB inhibition	Presumptive cord formation		ICT for MPT64 Antigen	
	Positive	Negative	Positive	Negative
MTB Complex	438	11	444	5
NTM	3	32	1	34

Table 2 – Combined results of Presumptive cord formation and MPT64 Antigen ICT assay in culture positive MGIT tubes.

Result	MTB	NTM
Cord positive ICT positive	433	0
Cord negative ICT positive	11	1
Cord positive ICT negative	5	3
Cord negative ICT negative	0	31
Total	**449**	**35**

Table 3 – Comparison of results for identification of MTB complex in liquid culture by Presumptive cord formation in smear, MPT64 Antigen ICT assay and combination of Presumptive cord formation and MPT64 Antigen ICT assay.

Parameter	Presumptive cord formation in smear	MPT64 antigen assay	Intersection of presumptive cord formation cord formation and MPT64 antigen assay	Union of presumptive cord formation and MPT64 antigen assay
% Sensitivity	97.6 (95.7–98.8)	98.9 (97.4–99.6)	96.4 (94.3–97.9)	100 (99.2–100)
% Specificity	91.4 (76.9–98.1)	97.1 (85.0–99.5)	100 (89.9–100)	88.6 (73.2–96.7)
% PPV	99.3 (98.0–99.6)	99.8 (99.8–99.9)	100 (99.1–100)	99.1 (97.8–99.8)
% NPV	74.4 (58.8–86.5)	87.2 (72.6–95.7)	68.6 (54.1–80.9)	100 (88.7–100)

Figures in bracket indicate 95% Confidence Interval limit.

NTM. Rapid speciation of these isolates, at least to the level of MTB complex vs NTM, is therefore necessary before proceeding to drug susceptibility testing.

Identification of isolated mycobacteria in liquid culture can be done using PNB inhibition test. PNB concentration of 500 μg/ml inhibits growth of mycobacteria belonging to MTB complex while NTMs show either slight or no inhibition. The accuracy of the test to differentiate MTB complex from NTM strains in MGIT culture has been reported to be 99.4%.[11] The test although sensitive and specific requires additional time of 4–11 days from the detection of a positive culture to the identification of an isolate.[3,11]

Members of MTB complex, when grown in liquid medium, often displays characteristic serpentine cording. The presumptive identification of MTB complex based on visualization of serpentine cording by ZN stain could potentially decrease laboratory turn-around time for result reporting without an increase in cost, since a smear must be made from positive liquid culture to determine if acid-fast organisms are present.[5] In our study, presumptive cord formation test had the sensitivity, specificity, PPV and NPV of 97.6%, 91.4%, 99.3% and 74.4%, respectively in comparison to PNB inhibition test. The test misidentified 11 (2.4%) MTB complex isolates as NTM resulting in lower NPV. Three NTMs (9.3%) were also misidentified as MTB complex leading to false positive results. Similar findings were also described by Kadam et al. in a study from India.[5] The false positive results are due to formation of true cords or pseudocords, that are loose aggregate of bacilli, by certain NTMs in liquid media. Presumptive cord formation test is therefore not recommended as the only test for identification of MTB complex.[5]

Tuberculosis MPT64 antigen is secreted only by viable & actively dividing cells of members of MTB complex.[12] ICT assay that detects the antigen by specific monoclonal antibody have been developed for use on both solid and liquid culture. Several kits are commercially available including SD Bioline TB Ag MPT64 rapid (Standard Diagnostics Inc., Korea), BD MGIT™ TBc Identification Test (Becton Dickinson and Company, USA) and Capilia TB (TAUNS Izunokuni, Japan) costing between INR 150-250 per test. In contrast, the PNB inhibition test on MGIT costs approximately INR 550 per test.[3] In the current study, the ICT assay had sensitivity, specificity, PPV and NPV of 98.9%, 97.1%, 99.8% and 87.2%, respectively in comparison to reference standard. Few authors have reported NPV of 100% contrary to our observations.[13,14] In our study, five MTB complex isolates on MGIT culture were misidentified by ICT assay. Ngamlert K et al. using Capilia TB ICT kit detected false negativity in 6 MTBC isolates out of 232 that were confirmed as positive by biochemical testing and molecular methods.[15] This may be attributed to mutations within the MPT64 gene leading to production of incomplete protein, as described by Hirano et al., that made identifying them difficult.[9] False negativity may be also due to the low expression of the MPT64 antigen by some isolates.[16] Main advantage of ICT assay is that it is rapid giving results only in 15 min. The assay is easy to perform and does not require any instrumentation or technical expertise.

To reduce the false negative and positive rates, presumptive cord formation in smear and ICT for MPT64 antigen assay were combined for MTB complex identification. When the results of the two tests were combined, the sensitivity and the NPV were both 100% for the intersected results, and the specificity and the PPV were 100% for the combined. These results are similar to those observed by Shen et al. combining cord morphology with the Capilia TB assay for identification of MTB in MGIT positive tubes.[8,17] We therefore suggest that when the cultured smear shows serpentine cord morphology and is also found to be positive by ICT for MPT64 antigen, the culture can be reported to contain MTB complex. If both the presumptive cord formation and the ICT for MPT64 antigen test are negative, the culture should be reported to contain NTM. However, when the serpentine cord is found in the smear but the ICT for MPT64 antigen is negative, or vice versa, further evaluation is necessary to ensure an accurate diagnosis.

5. Conclusion

Presumptive cord formation and ICT for MPT64 antigen assay can be used in combination as a simple, rapid and cost effective method for identification of MTB complex in clinical isolates obtained in liquid media. Only when discrepant results are obtained by the two tests, further evaluation is necessary to ensure an accurate diagnosis.

Conflict of interest

All authors have none to declare.

Contribution details

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b. Conduct of Study: Nikhilesh Kumar, A Agarwal, TN Dhole.

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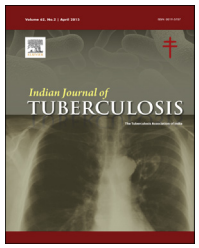

Original Article

Home based care to multi-drug resistant tuberculosis patients: A pilot study☆

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ABSTRACT

Background: India is a high tuberculosis burden and large population setting country. Multidrug-resistant tuberculosis patient has to undergo 24–27 months treatment and is expected to adhere to it. There is a need to increase compliance of MDR Regimen in MDR-TB cases, to prevent its further spread. The present study focuses on describing the role of home care support with counseling in the outcome of MDR-TB patients, in Delhi, India.
Material and methods: This is a prospective study carried out at a Community Health Centre, Delhi, involving 113 MDR-TB patients as and when they got registered with DOTS Plus centres, in two government hospitals of Delhi between August 2009 and March 2010. The study period was August 2009 to October 2012. These patients received daily MDR Regimen from their respective DOTS Providers. The patients' names and addresses were taken from the lists supplied by these hospitals. Final analysis was carried out for 101 MDR-TB cases.
Results: Out of 101 patients treatment outcomes were: 69.3% cured and 2.0% treatment completed (treatment success rate 71.3%). A low default rate of 6.9% was seen which is assumed to be due to the home based care.
Conclusion: These results indicate that Home based care with counseling support is an important intervention in management of MDR-TB patients and it needs to be substantiated by further research.

1. Introduction

Many countries participating in a global survey of anti-TB drug resistance, registered cases of MDR-TB by mid-1990s.[1] The revised Global Plan to Stop TB, 2006–2015 aims to reach universal access to sound management of MDR-TB and XDR-TB by 2015 in all countries; and near-to universal access in the 25 countries with high burdens of MDRTB and XDR-TB by

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2010.[2] The MDR TB services in India were initiated in 2007 in Gujarat and Maharashtra.[3] The Government of India's Revised National Tuberculosis Control Programme (RNTCP) uses regimen for MDR-TB which lasts for 6–9 months of the Intensive Phase and 18 months of the Continuation Phase.[4] As treatment course is long, expensive, and more toxic second line anti-TB drugs are used, this leads to low treatment success and high loss-to-follow-up rates. Thus retention and adherence to therapy are major challenges in treatment of MDR TB patients. In a study in India Dhingra et al reported a successful outcome only in 48% patients.[5] Default rates over 15% are found in several countries including Korea (32%),[6] Taiwan (29%),[7] Russia (20%),[8] Italy (17%),[9] Spain (16%),[10] South Africa (29%),[11] Argentina (20%),[12] and Peru (19%).[13]

'Treatment literacy' is one of the successful strategies to enhance adherence to anti-retroviral. Patients and families can only shoulder such a responsibility if they are informed. This approach has been endorsed by human rights organizations that recognize that patients have rights but when empowered also have responsibilities.[14] In a South African study an integrated home based treatment for MDR TB and HIV ensured high levels of treatment compliance with adherence support[15] and immediate adverse event monitoring and management.

Oyieng'o et al provided home treatment for MDR TB patients in Kenya and advocated that their program addressed both patient needs and health system needs.[16]

Our hypothesis is that the 'Home based support with counseling' gives opportunity to educate patient and care taker that ensures retention and adherence to therapy. Thus our study objective is to study the role of comprehensive home based care and support with counseling in the outcome of MDR-TB patients, in Delhi, India.

2. Material & methods

2.1. Study setting and patient selection

This is a prospective study carried out at a Community Health Centre, Delhi, involving 113 MDR-TB patients as and when they got registered with DOTS Plus centres, in two government hospitals of Delhi between August 2009 and March 2010. The study period was from August 2009 to October 2012.

These patients received daily MDR Regimen from their respective DOTS Providers. The patients' names and addresses were taken from the lists supplied by these hospitals.

2.2. Study design

A prospective study of 113 MDR-TB cases.

2.3. Inclusion and exclusion criteria

2.3.1. The inclusion criteria

- All MDR TB patients from Northeast, East, Central and West districts of Delhi, whose names appeared on the lists provided by LN Chest Clinic and who gave consent for participation.

2.3.2. Exclusion criteria

- Patients who refused consent.
- Very sick patients.
- Patients who could not be found on first visit (already dead or defaulted).

The 113 MDR-TB patients from the lists provided time to time by above mentioned hospitals were selected as our sample. As these patients belonged to the districts mentioned above this was a convenient sampling method. Out of these 2 had to be excluded from the study as they were very sick and remained in hospital for several months and there was no chance of giving home care to them. Another 7 and 3 MDR-TB cases had to be excluded as they were either dead or had already defaulted at the time of first visit of home care teams. Thus finally the analysis was carried out for remaining 101 MDR-TB cases.

2.4. Informed consent

An informed written consent in Hindi was taken from each MDR-TB patient before enrolling her/him in this study.

2.5. The tool

A proforma was prepared and discussed with stakeholders such as State TB Officer, WHO TB Consultant, Medical Superintendent and Nodal Officer TB of a Govt. Hospital.

2.6. Home care support teams

Two mobile multi-disciplinary teams of home care providers – Health educator cum care giver and a Team assistant cum care giver were developed. Each team had one male and one female worker. The team members were either Multipurpose Health Workers or Intermediate/Graduate with experience of working in the community. The junior team members were trained home care health attendants with working literacy.

The teams were trained using various RNTCP TB modules. The training included knowledge of tuberculosis, RNTCP, DOTS[17] and MDR TB.[18] They were also made aware of treatment of MDR-TB, its adverse drug reactions, natural history of the disease and co-morbidities. Skills training in communication and counseling was given by a registered NGO. Training in basic care of chronic patients such as back care, dressings, oral and general hygiene and sanitation, nutrition was imparted. Emphasis was laid on personal protection of the team members.

2.7. Home care support

Most of the patients were quite depressed and hopeless when they had to start MDR treatment because they had already taken several months CAT I and CAT II treatment earlier and had failed to get cured. Many patients had to leave their jobs due to TB and faced financial problems.

The teams made home visits in every 15 days in intensive phase and every 45 days in continuation phase. They spent

more than 30 min with each patient after the initial visit of 60–90 min. During home visits following was done:

2.8. Physical and mental support

2.8.1. Counseling

Home care teams spent a lot of time on providing psychosocial support to patients and their family members especially the care taker by counseling about the disease, DOTS plus treatment, importance of treatment adherence, TB transmission, coughing etiquette, proper disposal of sputum and the adverse drug reactions that patient could face. All the patients were given opportunities to talk about their emotional needs and problems. The teams lighted a ray of hope in these patients by motivating them to continue DOTs Plus treatment.

2.8.2. Hygiene and nutrition counseling

Patients neglecting personal hygiene were counseled. They were asked to keep their rooms properly ventilated by keeping door and window open during day time. Teams educated them about importance of balanced diet and high protein diet and emphasized that patients must take regular meals and try to increase his/her intake per meal. If a patient was from a very poor socio-economic background, the teams provided free multigrain biscuits and arranged one egg per day for him/her.

2.8.3. Nursing care

Massage for joint pain and application of cold compresses or dressing for injection site was provided at home to patients who required it.

2.8.4. Support at the time of ADRs

The teams took the patients in confidence and gave them their mobile telephone numbers so that patients could get help of teams 24 × 7. Once the team members got any information about early warning symptoms or adverse drug reactions they informed the consultant of study institution. The consultant then contacted nodal TB officers of either of the two Govt. hospitals and asked teams to refer/take patients to general government hospitals or Institute of Human Behavior and Allied Sciences (IHBAS) for ADRs as per the instructions of nodal officers. In the government hospitals nodal TB officers took prompt action and patient got special attention for her/his problems. This increased the motivation and compliance. Thus a lot of patients were prevented from becoming defaulters.

2.9. Vocational rehabilitation

Patients were quite depressed, hopeless weak and not confident of themselves but the teams through their psychosocial support encouraged them to do some work thus they re-started earning. School/college drop-out student-patients were also supported psychologically. Teams motivated and got them re-admitted into schools/colleges. Thus patients were brought to normal stream of life.

2.10. Financial rehabilitation

Teams created awareness about Rs. 300/per month financial support under Govt. TB Scheme, and helped getting them registered under it. Though this was a small amount but it helped patients.

3. Co-ordination with RNTCP

The teams visited DOTS Plus centres and contacted DOTS cum HIV Providers, Senior-Treatment-Supervisors (STSs) and/or District TB Officer (DTOs), to get a feedback on the progress of patients. They enquired about the results of sputum cultures. Data Tri-angulation on defaulters was achieved from the laboratory register, TB register and patient treatment cards. The teams also attended monthly meetings held at Lok Nayak Chest Clinic, to get more information about patients and to inform Nodal Officer TB, if there were any problems concerning the patients. In our study "treatment" includes "MDR treatment" as well as "Home care and Counseling Support" and the definition of "treatment outcomes" are those of DOTS-Plus Guidelines 2010.

4. Results

Hundred and one (101 MDR-TB patients 60 males and 41 females) were enrolled in this study. Sixty six percent of males & eighty three percent of females were below 41 years of age. Their demographic characteristics are shown in Table 1.

4.1. Home visits

Teams could visit (74.3%) of patients >5 times in Intensive Phase as their names and addresses were received at the start of treatment. Sixty six percent patients were visited 12 or more times in Continuation Phase and 68% were visited 18 or more times during the whole course of treatment.

4.2. Home care support with counseling

Hundred percent patients received counseling support. Eighty two percent of patients were provided nutritional support. The teams provided nursing care for injection abscess to 15% patients, care for emotional problems to 6%, supported 14% in case of ADRs by Hospital admissions. They supported 28% patients in getting Rs. 300 under the Govt. TB Scheme (this scheme lasted till the year 2009).The teams were instrumental in rehabilitating 10% patients by way of motivation to re-start employment and 7% in bringing back to school/college Table 2.

4.3. Adverse drug reactions (ADRs)

As shown in Table 3, the frequent ADRs were joint pains 41.6%, weakness 22.8%, nausea & vomiting 20.8%–21.8%, anxiety 15.8%, tremors12.9%, and giddiness10.9%.

Table 1 – Demographic characteristics of MDR-TB patients.

Age in years	Male (%)	Female (%)	Total (%)
Age & sex wise distribution			
0–15	–	3 (7.3)	3 (3.0)
>15–<21	8 (13.3)	11 (26.8)	19 (18.8)
>21–<31	19 (31.7)	13 (31.7)	32 (31.7)
>31–<41	13 (21.7)	7 (17.1)	20 (19.8)
>41–<51	8 (13.3)	4 (9.8)	12 (11.9)
>51–<61	11 (18.3)	1 (2.4)	12 (11.9)
>60	1 (1.7)	2 (4.9)	3 (3.0)
G. Total	60 (100.0)	41 (100.0)	101 (100.0)
Religion			
Hindu	50 (83.3)	34 (82.9)	84 (83.2)
Muslims	10 (16.7)	6 (14.6)	16 (15.8)
Sikhs	–	1 (2.4)	1 (1.0)
Caste			
Scheduled Caste	14 (23.3)	8 (19.5)	22 (21.8)
Scheduled Tribe	7 (11.7)	7 (17.1)	14 (13.9)
Other Backward Classes	4 (6.7)	–	4 (4.0)
General/Others	34 (56.7)	22 (53.7)	56 (55.4)
Caste not remembered	1 (1.7)	4 (9.8)	5 (5.0)
Education of head of family			
Postgraduate/Graduate	6 (10.0)	6 (14.6)	12 (11.9)
Intermediate	6 (10.0)	3 (7.3)	9 (8.9)
High School	10 (16.7)	3 (7.3)	13 (12.9)
Secondary	8 (13.3)	6 (14.6)	14 (13.9)
Primary	17 (28.3)	6 (14.6)	23 (22.8)
Illiterate	13 (21.7)	17 (41.5)	30 (29.7)
Occupation of head of family			
Clerk/Shop/Farmer	5 (8.3)	4 (9.8)	9 (8.9)
Skilled	14 (23.3)	9 (22.0)	23 (22.8)
Semi-skilled	9 (15.0)	5 (12.2)	14 (13.9)
Unskilled	15 (25.0)	9 (22.0)	24 (23.8)
Unemployed	17 (28.3)	14 (34.1)	31 (30.7)
Family income in Rupees			
>19575	–	1 (2.4)	1 (1.0)
9788–19574	7 (11.7)	6 (14.6)	13 (12.9)
7323–9787	4 (6.7)	4 (9.8)	8 (7.9)
4894–7322	16 (26.7)	3 (7.3)	19 (18.8)
2936–4893	16 (26.7)	15 (36.6)	31 (30.7)
980–2935	9 (15.0)	10 (24.4)	19 (18.8)
979	1 (1.7)	–	1 (1.0)
0	7 (11.7)	2 (4.9)	9 (8.9)

4.4. *Anthropometry*

As the treatment is dependent on the initial weight of patient, 64.4% weighed <45 kg. A statistically significant difference (p-value = 0.005; Student's paired t-Test) was found in these patients at the end of treatment as only 46.5% weighed <45 kg.

4.5. *Co-morbidities and substance abuse*

Nine percent of patients had Diabetes mellitus, 2% were HIV positive, and 7% had Chronic Obstructive Pulmonary Disease. Twenty five per cent were tobacco users and 17% consumed alcohol.

4.6. *Treatment outcomes*

Our treatment outcomes showed 69.3% cured and 2.0% treatment completed thus making treatment success rate of 71.3%, only 6.9% defaulted, 16.8% died, 4.0% failed treatment and 1.0% was transferred out.

5. Discussion

In this prospective cohort of 101 MDR-TB patients, there were 59% males and the mean age was 33 ± 2.74 (range 14–65) years.

In a study 61.75% were males and mean age was 37 ± 19.90.[19] In another study the median age was 41.0 years (range 2–99) and 70.1% were males.[20] In an Indian study 77.5% were males and the mean age of patients was 33.25 ± 12.04 years.[21]

Six percent of our patients with emotional problems were shown at IHBAS. In a retrospective case series in Lima, Peru, the incidence of depression, anxiety and psychosis during MDR-TB treatment was 13.3%, 12.0% and 12.0%, respectively.[22]

The pattern of adverse drug reactions in MDR TB patients in our study was joint pains (41.6%), nausea & vomiting (20.8%–21.8%), anxiety (15.8%), depression (7.9%), tremors (12.9%), and giddiness (10.9%). Helen S. Cox reported adverse events as gastrointestinal disturbances (32%) and among the 80 adverse events attributed solely to Cycloserine, 32 (40%) were described as neuropathies, 22 (28%) psychoses and 10 (13%) acute depression.[23] The effective management of side effects is fundamental to MDR-TB and XDR-TB treatment without it adherence for the full duration of treatment is unlikely[24] and this was possible in our intervention as 14% cases of severe drug reactions were supported by hospital admissions.

According to our study 69.3% patients were cured and 2.0% completed treatment (treatment success rate 71.3%) and only 6.9% defaulted. In a study in Beijing by Cui Hua Liu et al 53.4% MDR-TB patients had successful treatment,[10] in Uzbekistan (62%) were successfully treated (14%) default [(15%) died and

Table 2 – Support provided by home care teams.

	Male (%)	Female (%)	Total (%)
Counseling	60 (100.0)	41 (100.0)	101 (100.0)
Nursing care	7 (11.7)	8 (19.5)	15 (14.9)
Care for mental problems	2 (3.3)	4 (9.8)	6 (5.9)
Support in hospital admissions	9 (15.0)	5 (2.2)	14 (13.9)
Nutritional support provided	48 (80.0)	35 (85.4)	83 (82.2)
Support in getting Govt. TB Scheme money of Rs. 300/per month	14 (23.3)	14 (34.1)	28 (27.7)
Support in getting employment	10 (16.7)	–	10 (9.9)
Support provided in bringing back to school/college	1 (1.7)	6 (14.6)	7 (6.9)
Maximum number	60 (100.0)	41 (100.0)	101 (100.0)

Table 3 – Adverse drug reactions.

	Male (%)	Female (%)	Total (%)
Nausea	10 (16.7)	11 (26.8)	21 (20.8)
Vomiting	11 (18.3)	11 (26.8)	22 (21.8)
Hiccups	1 (1.7)	–	1 (1.0)
Abdominal pain	5 (8.3)	5 (12.2)	10 (9.9)
Black stools	1 (1.7)	1 (2.4)	2 (2.0)
Loss of appetite	–	1 (2.4)	1 (1.0)
Ringing in the ears	4 (6.7)	4 (9.8)	8 (7.9)
Hearing loss	1 (1.7)	–	1 (1.0)
Headache	2 (3.3)	6 (14.6)	8 (7.9)
Giddiness	3 (5.0)	8 (19.5)	11 (10.9)
Burning in micturition	2 (3.3)	1 (2.4)	3 (3.0)
Swelling of face & the feet	1 (1.7)	4 (9.8)	5 (5.0)
Sleeplessness	2 (3.3)	1 (2.4)	3 (3.0)
Anxiety	8 (13.3)	8 (19.5)	16 (15.8)
Depression	2 (3.3)	6 (14.6)	8 (7.9)
Altered behavior	–	1 (2.4)	1 (1.0)
Angry	–	1 (2.4)	1 (1.0)
Suicidal tendencies	–	–	–
Psychiatric problem	2 (3.3)	4 (9.8)	6 (5.9)
Tremors	4 (6.7)	9 (22.0)	13 (12.9)
Blurring of vision	5 (8.3)	5 (12.2)	10 (9.9)
Unusual bruising or bleeding	3 (5.0)	2 (4.9)	5 (5.0)
Joint pains	22 (36.7)	20 (48.8)	42 (41.6)
Dark colored urine	2 (3.3)	2 (4.9)	4 (4.0)
Jaundice	–	–	–
Skin rashes	3 (5.0)	7 (17.1)	10 (9.9)
Weakness	9 (15.0)	14 (34.1)	23 (22.8)
Body pain	4 (6.7)	3 (7.3)	7 (6.9)
Tingling	1 (1.7)	2 (4.9)	3 (3.0)

(9%) classified as treatment failures].[17] Green Light Committee Initiatives in their Annual Report 2009 [Global MDR Statistics 2000–2007] report 62.8% patients were cured, 11.5% Died, 8.0% Failed, 16.7% Defaulted and 1.0% Transferred out.[25] In a study in India - Gujarat and Maharashtra out of (43%) successfully completed treatment while (21%) defaulted.[4] Pauline Joseph et al in their study of 38 patients in Tamil Nadu reported (66%) as cured, (13.1%) defaulted, (7.8%) died and (13.1%) failed.[26] Arora et al in New Delhi found, that out of 28 patients, 67.9% were cured, 17.9% defaulted, 14.3% died, but one failed treatment.[27] As shown in our results the default and failure rates are low and treatment success rate is high as compared to other studies. These results indicate that Home based care with counseling support is an important intervention in management of MDR-TB patients and it needs to be substantiated by further research. The limitation of the study is that it was limited to only four TB districts of Delhi due to financial constraints.

Contributions of authors

Name of authors	Conception	Design	Acquisition of data	Interpretation of data	Drafting the article	Revising article for intellectual content	Final approval of version
1 Dr. (Mrs.) Joyce Felicia Vaghela	√	√	√	√	√		
2 Professor S.K. Kapoor		√				√	
3 Dr. Aditi Kumar				√			
4 Dr. Riti Das					√		
5 Dr. AshwaniKhanna					√		
6 Dr. Anuj K. Bhatnagar					√		

Conflicts of interest

All authors have none to declare.

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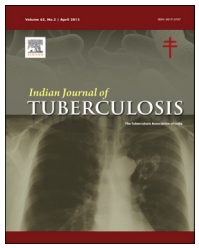

Original Article

A study on assessment of symptoms and functionality in DOTS cured patients in two districts of Garhwal, Uttarakhand

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ABSTRACT

Background: In 2013, an estimated 9.0 million people developed TB and 1.5 million died from the disease. India has achieved the target of a case detection rate of 70% and a cure rate of 85% through the nationwide Directly Observed Treatment Short Course (DOTS) strategy. Tuberculosis may generate residual lesions in the course of its pathology, which impair the functionality of the patient even after achieving "cure" or "treatment completion".

Aims: To assess the presence of symptoms and functionality of tuberculosis patients who had completed the treatment or had been declared as cured under Revised National Tuberculosis Programme (RNTCP).

Methods: The present study was a cross sectional study. It was conducted in the two Tuberculosis Units (TUs) of Rudraprayag and Pauri in Garhwal region of Uttarakhand among the people who had completed treatment under DOTS or had been declared as cured under RNTCP in last one year.

Results: Even at the completion of the treatment about 37% had cough, 25% had expectoration, 6% had hemoptysis, more than 50% had chest pain and 65% had breathlessness. The mean distance walked by the participants in six minutes was 363.5 ± 58.2 m with a range of 245–490 m.

Conclusions: The persistence of symptoms indicate that the functionality of DOTS cured patients remains compromised even after days and months of treatment completion, thereby necessitating measures for the improvement of the overall health of the patients rather than just the microbiological cure.

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1. Introduction

Tuberculosis causes ill-health among millions of people each year and ranks as the second leading cause of death from an infectious disease worldwide. WHO global report, 2014 shows that India accounts for 24% of the total cases of tuberculosis and ranks first among 22 high burden countries in terms of absolute numbers of incident cases each year.[1] India has achieved the target of a case detection rate of 70% and a cure rate of 85% through the nationwide Directly Observed Treatment Shortcourse (DOTS) strategy under the Revised National Tuberculosis Programme (RNTCP). However, considering the scenario of TB treatment, from the perspective of the patient, it is evident from studies that about one-third of the cured Pulmonary Tuberculosis (PTB) patients do have respiratory complaints at the end of treatment.[1,2]

Tuberculosis may also generate residual lesions in the course of its pathology, that impair the functionality of the patient even after achieving "cure" or "treatment completion".[3] Due to the current focus on achieving and maintaining the case detection rate and cure rate of tuberculosis patients as well as newly emerging issues of multi drug resistant tuberculosis and TB-HIV co-infection, the importance of achieving optimum functionality and relief from symptoms of respiratory illness and other systems of the body, that is associated with the chronic nature of tuberculosis, has not been realized in India.

Uttarakhand, situated in the lap of Himalayas, is a disadvantaged area due to geographical inaccessibility and consequent inaccessibility to medical and other basic services as well as compromised standard of living. Studies on the outcomes of the disease in the population residing in these areas are therefore not very common. The specific objectives of the study were to assess the presence of symptoms related to various systems of the body affected by tuberculosis, at different points during the course of treatment, as an indicator of the morbidity status or ill health. The study also intended to assess the addictions in the participants, the functionality of patients who had completed the treatment or had been declared as cured under RNTCP programme through the six minute walk test and also to study its association with various sociodemographic factors.

2. Material and methods

The present study was a cross sectional study conducted among the people who had completed treatment under DOTS or had been declared as cured under RNTCP. There are 13 districts in Uttarakhand which are grouped into two divisions, Kumaon and Garhwal. The present study was conducted in Garhwal division of Uttarakhand. The two districts selected from this region were Rudraprayag and Pauri. All the patients who had completed the treatment or had been declared as cured under RNTCP in the Tuberculosis Units (TU) of these two districts, in the last one year, from the month of data collection, were eligible for participating in the study.

3. Inclusion criteria

1. All those TB patients who have been "cured" or "completed treatment" under RNTCP during the last one year and are willing to participate in the study.
2. Subjects should be more than 18 years of age.
3. Subjects having any other diagnosed disease or other physiological condition such as pregnancy which would confine the results would be excluded from the study.

3.1. *Sample size and sampling procedure*

Assuming the prevalence rate of symptoms at the end of the treatment to be 50%, the sample size for the study was calculated using the formula

$$\frac{n = Z^2_{1-\alpha/2}\, pq}{L^2}$$

$Z_{(0.05)} = 1.96$
n = required sample size
p (prevalence rate of symptoms at the end of the treatment) = 50%
q = 1-p = 50% L = least permissible error (absolute precision)
L = 5%
Desired confidence level = 95%

$$\text{Hence sample size} = \frac{(1.96)^2 \times 50 \times 50}{5 \times 5} = 384$$

Since the size of the population i.e total number of patients in the two selected TUs who had completed the treatment in last one year were 80, which is less than the calculated sample size, following formula given by Kish, L (1965)[4] was used to calculate the final sample size:

$$\text{Sample size} = n/1 + (n/\text{population}) = 384/1 + (384/80) = 66.2$$

Therefore, a total of 68 patients were interviewed in the study.

3.1.1. *Duration of study*

The collection of data took place over a period of three months.

3.1.2. *Data collection, Instrument used confidentiality and quality control*

The address and contact numbers of the participants who had completed treatment in last one year was obtained from the

TB register at the TU. An appointment with the participants was scheduled and a convenient time was decided to meet them at their homes. The investigator then went to the house of the participant to conduct the interview. The interview was conducted only once and the details of symptoms before treatment, during treatment, at the completion of treatment and after treatment were recorded on the basis of recall by the participants. Written informed consent from all the participants was obtained prior to the commencement of the interview. For illiterate participants, the consent form was read out and thumb impression was obtained from them. Participants were told about the purpose of the study, the steps taken to assure confidentiality and informed that they could refuse to answer any questions or withdraw at any time if they are uneasy with the questions put to them. The data was collected by the same investigator to overcome interviewer bias.

3.1.3. *Study tool*

A pre-designed, pre tested questionnaire was used to collect data regarding the sociodemographic variables. The chronological progress of symptoms and signs during the treatment was based on that reported by the participants. The category and subcategory of treatment under which the participant was treated was obtained from the records at the TU.

3.1.4. *Statistical analysis*

Data was entered in Microsoft (MS) excel and analyzed using its data analysis tool pack of MS excel. For comparison of means independent sample t test was used and for comparison of proportions over different time periods, chi square trend was used.

3.1.5. *Ethical considerations*

For ethical considerations, permission was obtained from the Institutional Ethical committee of VCSGGMS&RI, Srinagar, Garhwal. Those participants, who reported the presence of symptoms at the time of interview, were advised to consult the medical officer in-charge of the District Microscopy Centre under which they were registered for further evaluation of their symptoms and treatment.

4. Results

4.1. *Sociodemographic details of the participants included in the study*

The mean age of the participants was 32.9 years with a range of 18–79 years. Fifty seven percent of the participants were males while the rest (43%) were females. All the participants were Hindu by religion. Majority of the participants were literate (92.7%) and had a median family income of Rs. 5000 per month. Forty seven percent of the participants were either students or were unemployed, while 28% were clerks/farmer/shop keeper. About one third of the participants were unmarried; the rest (64.7%) were married and cohabiting except one who was divorced/widowed.

4.2. *Details of tuberculosis disease in DOTS cured patients*

Three fourth of the participants were treated under category 1 while the rest (25%) were treated under Category 2 of DOTS regimen. Sixty percent of the participants were new sputum smear positive cases, while 15% participants had relapsed or had defaulted. About 12% of the participants had a family history of tuberculosis.

4.3. *Details of symptoms related to various body systems before, during and after treatment*

Data was collected regarding the various signs and symptoms related to the different systems of body affected by tuberculosis at various points of treatment duration, i.e. before treatment, during treatment, at treatment completion and after treatment completion. The general symptoms of fever (92.6%–10.3%), loss of appetite (94.1%–4.4%), loss of weight (83.8%–1.4%) and sleep disorders (51.4%–17.6%) were reported to improve majestically during the course of treatment. However, the fatigue (86.8%–72.1%) and pallor (52.9%–39.7%) experienced by the participants did not show much improvement in terms of percentage decline, yet it was found to be statistically significant. 10.3% of participants reported having fever even after the completion of treatment. Also 3 participants reported having insomnia with a sleep of only 2 hours per day. Forty five percent participants had continued gain in weight even after completion of treatment.

The respiratory symptoms also improved but not to a great extent and even at the completion of the treatment about 37% had cough, 25% had expectoration, 6% had hemoptysis, more than 50% had chest pain and 65% had breathlessness. Syncope or momentary fainting was also reported by 31% of the participants at the completion of treatment. The presence of respiratory tract infections (42.6%), cough (23.5%), expectoration (10.3%), chest pain (25%) and breathlessness (10.3%) and momentary fainting attacks (10.3%) continued even after the completion of treatment in some patients.

Palpitation increased marginally from 42.6% to 47.1% during the course of treatment and persisted in 27.9% participants even after completion of treatment. Similarly, cyanotic spells increased from 14.7% to 16.1% at treatment completion but did not continue later on. Visual disturbances were reported to increase from about 3% to 16% and continued in 3% participants.

In the gastrointestinal system, most of the symptoms such as heartburn, nausea and vomiting, pain in abdomen, abdominal distension and impaired gastrointestinal motility were reported to increase during the course of treatment but did not persist after the completion of treatment. None of the patients reported having jaundice at any point of time during the treatment.

Change in colour of the urine was reported by all the participants from the start till the end of the treatment. Dysuria also increased from 14.7% to 25%. Symptoms related to locomotor system such as pain in joints increased from 3% to

Table 1 – Prevalence of symptoms related to various body systems before, during, at and after treatment completion in DOTS cured patients.

Variables	Before treatment		During treatment		At the completion of treatment		After treatment		χ^2 (trend) value	p value[a]
	No.	%	No.	%	No.	%	No.	%		
General										
Fever	63	92.6	26	38.2	7	10.3	7	10.3	109.3	<0.0001
Loss of appetite	64	94.1	35	51.5	3	4.4	0	0	157.4	<0.0001
Loss of weight	57	83.8	23	33.8	1	1.4	0	0	130.9	<0.0001
Gain of weight	0	0	13	19.1	51	75	31	45.5	55.5	<0.0001
Fatigue	59	86.8	50	73.5	49	72.1	0	0	95.7	<0.0001
Pallor	36	52.9	30	44.1	27	39.7	0	0	40.3	<0.0001
Sleep disorder	35	51.4	28	41.1	12	17.6	3	4.4	45.1	<0.0001
Respiratory system										
Respiratory tract infections in last year	52	76.4	38	55.9	30	44.1	29	42.6	17.6	<0.0001
Cough	66	97.1	44	64.7	25	36.8	16	23.5	85.0	<0.0001
Expectoration	64	94.1	44	64.7	17	25	7	10.3	115.4	<0.0001
Hemoptysis	46	67.6	19	27.9	4	5.9	0	0.0	90.9	<0.0001
Chest pain	59	86.8	33	48.5	35	51.5	17	25	45.4	<0.0001
Breathlessness	53	77.9	54	79.4	44	64.7	7	10.3	66.1	<0.0001
Swelling of feet	2	2.94	0	0	0	0	0	0	3.6	0.056
Sinusitis/running nose	1	1.47	4	5.88	4	5.9	0	0	0.21	0.65
Syncope	20	29.4	13	19.1	21	30.9	7	10.3	4.1	0.04
Cardiovascular system										
Palpitation	29	42.6	31	45.6	32	47.1	19	27.9	2.6	0.11
Visual disturbances	2	2.94	5	7.35	11	16.1	2	2.9	0.38	0.53
Cyanotic spells	10	14.7	13	19.1	11	16.1	0	0	6.9	0.008
Gastrointestinal system										
Dyspepsia	8	11.8	8	11.8	3	4.41	3	4.4	3.9	0.046
Heartburn	4	5.88	21	30.9	16	23.5	3	4.4	0.35	0.55
Nausea/vomiting	3	4.41	1	1.5	12	17.6	2	2.9	0.77	0.38
Jaundice	0	0	0	0	0	0	0	0	–	
Pain abdomen	6	8.82	6	8.8	13	19.1	2	2.9	0.2	0.65
Haematemesis/Maelena	9	13.2	0	0	0	0	0	0	16.7	<0.0001
Diarrhoea/constipation	7	10.3	11	16.2	10	14.7	4	5.9	0.7	0.40
Distention of abdomen	15	22.1	21	30.9	18	26.4	0	0	10.6	0.001
Genito-urinary system										
Change in colour	68	100	68	100	68	100	0	0	163.2	<0.0001
Dysuria	10	14.7	17	25	17	25	0	0	4.9	0.03
Locomotor system										
Pain in joint	2	2.94	10	14.7	12	17.6	0	0	0.15	0.70
Burning pain in feet	0	0	3	4.41	0	0	0	0	0.6	0.43
Swelling in joint	0	0	3	38.2	0	0	0	0	0.6	0.43
Lymphoreticular system										
Palpable lymph nodes	1	1.47	2	33.8	13	19.1	9	13.2	10.8	0.001
Pain in bones	5	7.35	8	19.1	5	7.4	3	4.4	0.83	0.36

[a] p value<0.05 is considered to be significant.

17.6%. The palpable lymph nodes increased during treatment and decreased by the end of treatment but did not get cured completely (13.2%). The pain in bones also increased during the course of the treatment and then decreased down to the pretreatment levels at treatment completion, with only three participants having backache even after the completion of treatment (Table 1).

4.4. *Distribution of personal habits of addiction in DOTS patients*

The analysis about the personal habits of the participants at the time of interview showed that about two fifth of the participants were alcohol users and one fifth used to take alcohol twice a week. About 33% of the participants were ever or current users of tobacco, of which about 77% used smoked forms and 14% used smokeless forms of tobacco while 9% used both. The commonly used smoked form was *bidi*, which is a local and cheaper variant of cigarette. The users of smoked tobacco used about 11 packets per day on an average (Table 2).

4.5. *Six minute walk test distance (6MWTD)*

The mean distance walked by the participants in six minutes was 363.5 ± 58.2 meters (m) with a range of 245–490 m. The association of different variables with the 6MWTD did not

Table 2 – Distribution of addiction related variables in DOTS cured patients at the time of interview.

Personal habits		Number	Percentage
Previous/current alcohol use	None	44	64.7
	Daily	0	0
	Twice a week	14	20.6
	Weekly	3	4.4
	Monthly	4	5.9
	Occasionally	2	2.9
	Previously consumed for 25 years	1	1.5
Tobacco use	Never user	46	67.6
	Ever user	12	17.6
	Current user	10	14.7
Type of tobacco	Smokeless	3	4.4
	Smoke	17	25.0
	Both	2	2.9
Type of smoked form	Bidi	15	22.1
	Cigarette	3	4.4
	Both	2	2.9
Current user	Mean packets per day	11.4	

reveal any significant difference across various variables. However, the values of 6MWTD were better, albeit not significantly, in males, students/unemployed/unskilled/semiskilled workers, never married, category 1 patients and never users of alcohol and tobacco when compared to the other groups (Table 3).

5. Discussion

The present study aimed to assess the prevalence of symptoms related to various systems of the body in cured patients of tuberculosis, their addictions and the association of various sociodemographic factors and disease related variables with the functionality of the participants. The analysis of sociodemographic factors shows that the participants were mainly from the productive age groups with a mean age of 33 years. The gender wise distribution of TB and the occupational distribution were in accordance with another study conducted in Gwalior in 2006[5] and in Delhi.[6] However the literacy rates in the present study were higher as compared to these studies. The fact that all the married participants were cohabiting indicates the acceptance of the tuberculosis patients in their family.

The distribution of the category of DOTS patients in the present study was in accordance with that of other similar studies conducted in India[5] as well as the national figures like National Family Health Survey 3 (NFHS 3).

It was very disheartening to observe that about 15% of the participants were current users of tobacco in either smoked or smokeless form. Also, two fifth of the participants were alcohol users and one fifth of them took alcohol biweekly adding to the liver damaging effects of the anti-tubercular drugs. Another study done at TRC Chennai also reported the prevalence of smoking and alcohol to be 50% and 38% respectively in the patients who had been cured of TB.[7]

Several studies have described the hindering process of the addictions on the treatment outcomes of TB in the form of reduced compliance and treatment failure as well as increased contagiousness. Suffering from alcoholism and chronic medical illness further contributes to a cycle of poverty, displacement and socioeconomic disempowerment that often makes recovery unattainable, even for the most motivated patients.[8–10] Efforts should be made for eradication of these addictions and for maximizing the benefits of the antitubercular drugs while simultaneously reducing the side effects of the drugs.

The focus of the global and national strategies for TB control is case detection and treatment completion for reducing the transmission of disease to others and consequently decrease the burden of disease; the effect that the disease and the drugs have on the patient who is suffering with the disease is largely neglected with no provisions in the programme framework for their recovery to optimal state of health. Moreover, after the completion of treatment, no clinical evaluation of the patient is done to see if the patient has recovered clinically also, along with microbiological cure from the illness. It has been a common observation that many patients report the persistence of symptoms after the completion of treatment and achievement of the "cured state" from the disease and this was well evident from the findings of the present study also. In another study done to assess the impact of TB one year after the successful completion of treatment, it was observed that 40% of these people reported persistent symptoms, such as breathlessness, cough, chest pain, and occasional fever.[9,11]

A study conducted at TRC, Chennai, during August 2004–2005 in patients who had been sputum negative at the 60th month of follow up, reported that, 29% of the participants investigated, had persistent respiratory symptoms; 86% had radiological sequelae but none had active disease. Abnormal PFT was observed in 65% with predominantly restrictive type of disease in 45%. These findings corroborate with the findings of persistent symptoms in the present study.[7]

The persistence of general and respiratory symptoms as well as the presence of visible signs of TB in the form of lymph nodes even after the completion of the treatment adds to the compromised quality of life of the patients as well as the

Table 3 – Association of 6 minute walk test distance with sociodemographic, treatment and addiction related variables in DOTS cured patients.

Variables		Mean (m)	Standard deviation (m)	t test for equality of means (independent samples test)				
				t statistic	Sig (2 tailed)	Mean difference	95% CI of the difference	
							Lower	Upper
Overall mean		363.53	58.18					
Gender	Male (39)	370.31	60.90	1.12	0.268	15.89	−12.54	44.32
	Female (29)	354.41	54.0					
Locality	Urban (45)	362.82	59.48	−0.14	0.89	−2.09	−32.08	27.90
	Rural (23)	364.91	56.84					
Occupation	Student/unemployed/unskilled worker/semiskilled worker (11)	326.55	53.76	2.38	0.020	44.12	7.13	81.11
	Skilled worker/clerk/shopkeeper/farmer/semiprofessional/professional (57)	370.67	56.69					
Marital status	Never married (23)	380.35	71.32	1.73	0.09	25.41	−3.931	54.76
	Married & cohabiting/Divorced/Widowed/Others (45)	354.93	48.87					
Category of DOTS treatment	Category 1 (51)	367.86	59.77	1.06	0.29	17.33	−15.17	49.84
	Category 2 (17)	350.53	52.67					
Previous/Current Alcohol use	Never (44)	372.64	58.37	−1.77	0.08	−25.80	−54.82	3.21
	Ever (24)	346.83	55.15					
Tobacco use	Never user (46)	372.04	55.11	−1.77	0.08	−26.31	−55.96	3.33
	Ever user/current user (22)	345.73	61.66					

Sig(2 tailed) value<0.05 is considered to be significant, df (degree of freedom) = 66.

social stigma due to the evident signs and symptoms of disease. Most of the symptoms decreased during the course of treatment but did not disappear altogether even at the end of the treatment indicating an incomplete cure as far as symptomatic recovery from disease is concerned. These symptoms seemed to gradually disappear in due course of time. Also, almost all the gastrointestinal symptoms increased during the course of treatment, adding to the agony of the patient. The goal of microbiological cure is therefore transitional and should be extended to cater to the alleviation of persisting agonizing symptoms which impede the progress of the patient to optimal health.

A study by Di Naso FC[12] has reported higher mean Six Minute Walk Test Distance (6MWTD) (484.21 ± 74.01 m) as compared to the present study. Also, 6MWTD in men (502.0 ± 43.0 m) and women (502.0 ± 43.0 m) was reported to be higher in other study.[13] No significant association of 6MWTD was observed with various variables assessed in the present study. Other researchers have however found that respiratory impairment was significantly higher in females and smokers.[7] These studies have assessed the 6MWTD in patients with active TB or at the end of treatment but we assessed it after a gap of at least few months of treatment completion. Despite the time gap, the reduced 6MWTD observed in our study is discouraging and does not seem to support the hypothesis that the lung and cardiovascular capacity of people living at hill regions is better thus providing them with better chances of rehabilitation. Interventions for improving the functionality of the patients suffering from TB need to be incorporated in the programme.

6. Conclusions

With the achievement of the goals of case detection and treatment in RNTCP, it's time to shift the focus on optimizing the health status of the patients suffering or having suffered from TB for bringing about an improvement in overall health of the patients.

7. Limitations

The inability to use a control group or to conduct a prospective study for obtaining the baseline clinical signs and symptoms to assess the change in the signs and symptoms, due to the constraint of time and man power, has been a major limitation of the present study. There is also a probability of recall bias in assessment of the symptoms of the patients during the illness. The objective assessment of signs and symptoms experienced by the patients before, during and after the completion of treatment would add to the validity of the observations about the persistence of symptoms related to TB. Also, the results of the study should be generalized carefully as it has covered only two districts. However the results seem to be valid enough for the two districts included in the study and can be extrapolated to patients with similar background characteristics.

Conflicts of interest

All authors have none to declare.

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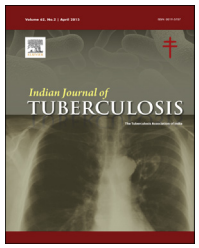

Original Article

Leptin level correlates with obesity and health related quality of life in obstructive sleep apnea syndrome patients

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ABSTRACT

Background: Leptin takes part in regulation of energy balance, neuronal functions, pain and mood. It may act as intermediary marker for various components of HRQOL in patients of obstructive sleep apnea syndrome.
Aims: To document the correlation among leptin levels, obesity and HRQoL in OSAS patients.
Methods: A tertiary care hospital based cross-sectional study was done in 224 subjects aged 18–65 years, after taking informed consent. Subjects with previous history of smoking, Liver disease, COPD, CHD, T2 DM, asthma, cancer, end stage renal disease, heart failure, any endocrine disorder including Cushing syndrome, thyroid, on systemic steroid or any continuous medication for last 6 months, on dieting or suffering from any disability condition (other than obesity and OSAS) affecting their HRQoL were excluded from the study. All subjects underwent Polysomnography. Leptin assay was done by ELISA method. Hindi version of HRQoL tool SF-36 was used to evaluate HRQoL.
Results: SPSS 20 was used to analyse data. Three groups (AHI <5, 5 to 15 and >15) were compared. Significant differences were observed in BMI, NC, WC, WHR and ESS. Differences were not significant in sleep architecture and Leptin level. SF-36 HRQoL, scores were observed decreased with increase in severity of disease. Leptin level was found significantly correlated with "Role limitations due to physical health problems", "Social functioning", Hypopnea and obesity indices.
Conclusions: In these subjects Obesity indices are the most important correlates of Leptin level. Oxygen desaturation indices with exception of Hypopnea and HRQoL may not be exclusively correlated to leptin levels.

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1. Introduction

Obstructive Sleep Apnea Syndrome (OSAS) is characterized by difficulties in breathing during sleep and associated physiological and metabolic abnormalities resulting from disturbed sleep. This condition afflicts 4% of men and 2% of women.[1] Patients experience loud, heavy, and repetitive snoring and chronic fatigue. Disrupted sleep, nocturnal arousals and Excessive Daytime Sleepiness (EDS) are some other important symptoms. It poses detrimental effects on physical and mental functioning. The effects of sleep disorders on the quality of life (QOL) have been documented in the literature.[2–4]

Leptin is a cytokine-like hormone. It is produced in adipose tissue and takes part in regulation of energy balance and in a range of other processes via actions in the central nervous system.[5] Leptin activates its cognate receptor primarily on the central nervous system by binding them.[6] Circulating leptin levels reflect the quantity of energy stored in adipose tissue and are correlated to the body mass index (BMI) in humans.[7] Leptin has a variety of other key central and peripheral functions to regulate metabolism, fertility and bone metabolism.[8] Leptin has peripheral actions to stimulate oxidative stress, vascular inflammation and vascular smooth muscle hypertrophy that may contribute to pathogenesis of type 2 diabetes mellitus (T2DM), High Blood Pressure, atherosclerosis and coronary heart disease (CHD).[9–11] Obesity is recognized to be an important risk factor for occurrence and worsening of OSAS. Obesity itself has a major role concerning deterioration in quality of life. Approximately 70% of cases with this disease are obese.[12]

Leptin also has a broad role in the regulation of neuronal functions, nociceptive behavior and neuropathic pain.[13] Neuronal leptin receptors are expressed across functionally well equipped areas of brain which includes the hypothalamus, thalamus, cortex, hippocampus, amygdala and in the dorsal root ganglion which are implicated in the control of mood and emotion. This expression pattern is consistent with leptin's feeding behavior, tissue inflammation and other extensive neuronal functions. Leptin may also mediate depressive symptoms.[14,15] Thus Leptin may perform as intermediary marker for various components of HRQOL in patients of obstructive sleep apnea syndrome.

The purpose of the present study was to document the correlation among leptin levels, obesity and HRQoL in OSAS patients.

2. Material and methods

Two hundred twenty four male subjects aged between 18 and 65 years were enrolled in the study after taking written/informed consent. This tertiary care hospital based cross-sectional study was conducted between November 2010 and May 2014 after obtaining ethical clearance from university research ethics committee. Subjects with previous history of smoking, Liver disease, COPD, CHD, T2 DM, asthma, cancer, end stage renal disease, heart failure, any endocrine disorder including Cushing syndrome, thyroid abnormalities, on systemic steroid or any continuous medication in last 6 months, on dieting or suffering from any disability condition (other than obesity and OSAS) affecting their quality of life were excluded from the study.

2.1. *Polysomnography*

Full night Polysomnography was carried out with S-7000, Cogent technologies, EMBLA System Inc, which includes Electroencephalograms (EEG), (C3-A2,C4-A1,O2-A1,O3-A2), Bilateral Electro-oculogram (ROC,LOC), Chin and Leg Electromyogram, Nasal airflow, Thoracic and abdominal movements, ECG, Oxygen Saturation measurement by finger Pulse oximeter and body position recorders. Apnea Hypopnea Index was calculated with the help of Somnologica Studio software. The apnea episodes were defined as complete cessation of airflow for $\geq$10 s, and hypopnea was defined as a $\geq$50% reduction in oronasal airflow accompanied by a reduction of at least 4% oxygen saturation calculated by pulse oximetry. Apnea events were classified as obstructive, mixed, or central, according to the presence or absence of breathing efforts with thoraco-abdominal paradox. AHI was determined by the frequency of these events per hour during sleep time based on the results of the overnight polysomnography. Recorded Polysomnographic data was cross checked manually for scoring of sleep stages, apneas and Hypopnea events regarding each subject.

2.2. *Leptin assay*

Fasting venous blood samples were taken in a serum separator tube after completion of the overnight polysomnography study (within 30 minutes and between 07:00 to 08:00 AM) from all subjects. After clot formation, samples were centrifuged at 2000 $\times$ g for 10 minutes. Serum was removed and stored in deep freezer at -20 °C. Leptin assay was done by ELISA method (as per manufacturer's instructions of AviBion reagents kit).

2.3. *Evaluation of HRQOL (SF-36)*

The "SF-36" is a 36-item generic Health Related Quality of Life measure that assesses eight domains: 1) physical functioning (PF); 2) role limitations due to physical health problems (RP); 3) body pain(BP); 4) general health perception(GH); 5) vitality(VT); 6) social functioning(SF); 7) role limitations due to emotional health problems(RE), and 8) mental health(MH).[16] The SF-36 Health Survey was translated and validated in Hindi for the Indian population. Subjects came to sleep lab for polysomnography at 9:00 pm and were asked to complete the self-administered QOL SF-36 Health Survey an hour prior to overnight polysomnography. All scores ranged from 0 to 100, with a higher score indicating better QoL. Domains were analyzed separately. Hindi version of HRQoL tool SF-36 was used to evaluate PF, RP,BP, GH, VT, SF, RE, MH, Physical

Component Summary (PCS) and Mental Component Summary (MCS) in these subjects.

2.4. *Statistical analysis*

Statistical Analysis was performed using SPSS 20 (SPSS Inc, USA). After assessing for approximate normal distribution, all continuous variables were summarized as mean ± SD and comparison between groups was done with one way ANOVAs test followed by the Tukey test. Pearson Correlation was applied to find correlation between different variables.

Three groups were made and compared (AHI <5, AHI 5 to 15 and AHI >15) consisting 44, 52 and 128 subjects respectively. Four subjects with AHI >30 were merged in AHI >15 group.

3. Results

On comparing mean values of three groups (AHI <5, AHI 5 to 15 and AHI >15), significant differences were observed in Body mass index (kg/m^2), Neck Circumference (inches), Waist Circumference (centimeters), Waist Hip Ratio and Epworth sleepiness scale. These differences were not significant in N1 (%), N2 (%), N3 (%), REM (%), Sleep efficiency (%) and Leptin level (ng/ml) (Table 1).

On evaluating all eight components and two summaries of SF-36 HRQoL, scores of PF, RP, BP, GH, VT, SF, RE, MH, PCS and MCS were observed decreasing with increase in degree of disease severity. Significant differences were found between different severity groups in PF and BP components score (Table 2). Significant differences were also found between three severity groups in PSC score (Table 2).

Pearson correlation was applied to find correlation between scores of components of SF-36 HRQoL with AHI, BMI, ESS and Leptin level. Significant negative correlation was observed between BMI and PF, RP, GH, VT, SF, MH and PCS scores (Table 3). Similar negative significant correlation was observed between AHI and PF, RP, GH and PSC scores (Table 3). A strong negative significant correlation was found between ESS and PF, BP, VT, SF and PSC score (Table 3).

Leptin level was found significantly negatively correlated with only RP and SF score in our study setting. Although a marginal non-significant negative correlation between leptin level and MSC score was distinguished (Table 3). Correlations of Leptin and other Oxygen Desaturation and obesity indices were analysed. Leptin was observed significantly positively correlated with Hypopnea events and strong significant positive correlation was also found between leptin and BMI, NC, WC, HC and WHR (Tables 4 and 5).

4. Discussion

To the best of our knowledge, this is the first study where comparison of components of HRQoL SF-36 with leptin levels in suspected OSAS subjects was done. We designed this study to minimize number of confounding factors[17] affecting circulating leptin concentrations in addition to body mass index in including subjects. This study clearly compares and defines OSAS-related disturbances (oxygen desaturation indices and Sleepiness), obesity indices and leptin levels with level of impairment in different components and summaries of HRQOL without interference of possible confounders. Obesity, OSAS severity and Sleepiness appeared as important determents of most of the components of physical health components including PSC of HRQOL.

Other than having its effect on hypothalamus, leptin has significant effects on neurogenesis, axon growth, synaptogenesis, denditric morphology, development of

Table 1 – Anthropometric, sleep parameters and leptin levels of subjects classified according to the severity of the disease.

Variable	AHI <5	AHI 5 to 15	AHI >15
Age (years)	39.7 ± 10.4	42.6 ± 9.7	46.7 ± 9.3
Body mass index (kg/m^2)	28 ± 2.3	29.3 ± 2.8*	31.5 ± 3.8#
Neck Circumference (inches)	15.4 ± 1	15.6 ± .9*	16.5 ± 1.2#
Waist Circumference (centimeters)	97.5 ± 7.9	104 ± 5.9*	110 ± 12.1#
Waist Hip Ratio	.99 ± .08	1.03 ± .03*	1.06 ± .06#
AHI (events/h)	1.5 ± .9	8.4 ± 2.3*	54 ± 24.2#*
Epworth sleepiness scale	7.4 ± 3.3	9.3 ± 5.7*	13 ± 4.8#
N1 (%)	13.8 ± 6.6	14.9 ± 12.4	23 ± 14.1
N2 (%)	40.8 ± 19.2	39.4 ± 24.3	37.9 ± 21
N3 (%)	21.8 ± 22.5	22.8 ± 21.4	22.9 ± 19.6
REM (%)	23.4 ± 20.3	22.8 ± 20.5	22.7 ± 23.9
Sleep efficiency (%)	63.9 ± 17.7	61.4 ± 18.3	55.1 ± 16.8
Leptin level (ng/ml)	6.1 ± 3.8	9.5 ± 6.9	10.3 ± 7.8
Number of subjects (n = 224)	**44**	**52**	**128**

Data values as means ± SD. REM = rapid eye movement; AHI = apnea hypopnea index.
*P < 0.05 compared to AHI <5; #P < 0.05 compared to AHI 5 to 15 (comparisons by ANOVA followed by the Tukey test).

Table 2 – Components and summery of SF-36 HRQoL of subjects according to the severity.

Components of SF-36 QOL	AHI <5	AHI 5 to 15	AHI >15
Number of subjects (n = 112)	22	26	64
Physical functioning	86 ± 12.2	60.7 ± 31.4*	55.3 ± 25.5#
Role limitations due to physical health problems	85 ± 26.8	65.3 ± 38.9	54.6 ± 37.8
Body pain	91.6 ± 11.3	66 ± 27.3*	67.2 ± 21.5+*
General health	57.2 ± 21.4	52 ± 23.5	42.6 ± 20
Vitality	67.5 ± 15.1	50.7 ± 26.1	50.1 ± 20.1
Social functioning	88.7 ± 21.1	80.7 ± 18.2	71.4 ± 27.7
Role limitations due to emotional health problems	83.3 ± 28.3	59.3 ± 42.1	52.1 ± 39.6
Mental health	66.8 ± 12.2	65.8 ± 14.7	60.3 ± 20.5
Physical components summery	51.9 ± 5.9	43.2 ± 10.3	38.9 ± 10#*
Mental components summery	48.6 ± 8.2	45.8 ± 12.7	47.1 ± 9.7

Data values as means ± SD.
*P < 0.05 compared to AHI <5; #P < 0.05 compared to AHI 5 to 15; +P < 0.05 compared to AHI >15 (comparisons by ANOVA followed by the Tukey test).

oligodendroglial cells, neuron excitability, neuroprotection and regulation of beta-amyloid levels. It has been proven that Leptin has a positive impact on cognition and mood in animal models of depression and anxiety. In non-obese humans, leptin levels alleviate the chances of development of Alzheimer's disease.[18] Thus Leptin may protect the brain against the development of mood and neurodegenerative disorders.

In previous studies increasing severity of OSAS was observed associated with increase in serum leptin levels[19] and sleep hypoxemia was observed as main determinant of circulating leptin levels.[20] On the other hand Shimura et al[21] demonstrated that circulating leptin levels correlated only with BMI, but not with PaO_2 or sleep mean arterial oxygen saturation. Similarly, in the Icelandic Sleep Apnea Cohort study by Arnardottir et al,[22] it was observed that leptin levels were more highly correlated with BMI and no relationship was found between sleep apnea severity and leptin levels, assessed within three BMI groups (BMI <30, BMI 30–35 and BMI $\geq$35 kg m^{-2}). Sánchez-de-la-Torre M et al[23] also observed that basal leptin level was mostly associated with obesity and found that sleep apnea was not a determinant factor in leptin levels. Interestingly, in same study they observed that nCPAP treatment diminishes leptin in obese OSA patients. Similarly Ursavas et al[24] also not found any significant difference in the levels of leptin, in OSAS group when compared to controls while observed a significant positive correlation between leptin and body mass index. They did not find any significant correlation between leptin and any polysomnographic parameters. Barceló et al[25] compared the levels of leptin in four groups, obese and nonobese with OSAS compared with obese and nonobese controls. They did not find any significant difference in the leptin levels between the groups. In another important study[26] carried out with Indian population, Sharma et al. found no significant difference in the levels of leptin in OSAS group and controls and at the same time there was not significant correlation among AHI, mean oxygen saturation in sleep, mean oxygen desaturation in sleep, oxygen desaturation index, and serum leptin levels. They only found a significant positive correlation between leptin levels and BMI.

Table 3 – Correlations of components of SF-36 HRQoL with AHI, BMI and leptin level.

Components	BMI	AHI	ESS	Leptin
	r Values			
Physical functioning	−0.45**	−0.27*	−0.21	−0.16
Role limitations due to physical health problems	−0.26*	−0.38**	−0.25*	−0.32**
Body pain	−0.21	−0.18	−0.36**	−0.15
General health	−0.36**	−0.27*	−0.17	−0.20
Vitality	−0.35**	−0.17	−0.34**	−0.20
Social functioning	−0.23*	−0.24	−0.47**	−0.27*
Role limitations due to emotional health problems	−0.15	−0.08	−0.08	−0.22
Mental health	−0.28*	0.07	0.08	−0.14
Physical components summery	−0.39**	−0.38**	−0.34**	−0.20
Mental components summery	−0.18	−0.01	−0.14	−0.25

* Correlation is significant at the 0.05 level.
** Correlation is significant at the 0.01 level.

Table 4 – Correlations of oxygen desaturation indices parameters and leptin level.

Variables	Correlation with leptin (r value)
AHI (per hour)	0.23
Obstructive events (per hour)	0.16
Hypopnea (per hour)	0.27*
Desaturation fall >5%	0.13
Average oxygen saturation	−0.19
Lowest oxygen Saturation	0.13
Average desaturation	0.24
SpO_2<90%	0.09

*Correlation is significant at the 0.05 level.

Table 5 – Correlations of obesity indices parameters and leptin level.

Components	Correlation with Leptin(r value)
BMI	0.33**
NC	0.30*
WC	0.38**
HC	0.34**
WHR	0.26*

*Correlation is significant at the 0.05 level.
**Correlation is significant at the 0.01 level.

Our findings are in accordance with these previous observations.[21–26]

Perhaps beneficial and protective effects of leptin become non-functional probably due to leptin resistance[27] or due to brain damage[28,29] caused by oxygen desaturation events in our subjects.

Physical Components Summery score of SF-36 HRQOL includes Physical Functioning, Role limitations due to physical health problems, Body Pain and General Health components. In current study, Leptin levels were observed significantly negatively correlated with only one component (Role limitations due to physical health problems) of Physical Components Summery of SF-36 HRQOL while overall Physical Components Summery was not found significantly correlated with Leptin levels. Similar non-significant correlation with body pain was also observed in a recent case-control study.[30]

Our data indicates that most of the HRQOL components except for "Social functioning" may not be exclusively correlated to leptin levels. It indicates a possible role of leptin resistance in affecting "mental health" of these subjects.

In conclusion, this study has shown that leptin could not be a useful potential marker of disease severity in patients with OSA and show no correlation to disease or oxygen desaturation indices with exception of Hypopnea events. However this cross-sectional study cannot be used to confirm cause-effect relationship between Hypopnea events and leptin levels. This is the first study revealing the effects of Hypopnea on leptin concentrations controlling or vice versa for fundamental influencing factors in healthy men. According to our data, plasma leptin levels seem to be unaffected by other desaturation indices. Future studies are desirable to further clarify the relationship between hypopnea events and

leptin regulation in physiological and pathophysiological states.

Conflicts of interest

All authors have none to declare.

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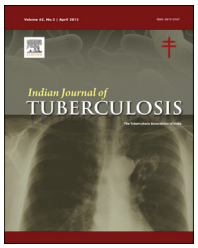

Case Report

Tubercular prostate abscess in an immunocompetent patient

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ABSTRACT

Prostate tuberculosis is an infrequent manifestation of genitourinary tuberculosis Complications like prostate abscess, perineal fistula, sinus can occur in immunocompromised individuals. Various predisposing factors like diabetes, bladder outlet obstruction, chronic renal failure can lead to prostate abscess. TRUS (Transrectal USG) is one of the tools useful for the diagnosis of prostatic abscess. We present our case, 57 year man, ethanolic with features of chronic liver disease and pulmonary tuberculosis which disseminated to prostate, developed abscess presenting as pyrexia of unknown origin.

1. Introduction

In India, the incidence of tuberculosis is 2.2 million/year.[1] Extra-pulmonary tuberculosis (E.P.T.B.) comprises 20–25 % total burden of the disease in which genito-urinary tuberculosis (G.U.T.B.) is 4%. The primary organ affected in the urinary tract is kidney. In the male genital tract, primary site of infection is epididymis followed by seminal vesicle, prostate, vas deferens and testis.[2] Many cases of prostate tuberculosis have been reported in the literature. Route of infection may be either hematogenous or descending. In most of the cases, primary focus of infection may not be demonstrated. In immunocompetent individuals, GUTB occurs 8–39 years after pulmonary tuberculosis.

Most frequent complication of prostate tuberculosis is infertility due to destruction of glandular tissue and reduction in the ejaculatory volume of semen. Less frequent complications are prostate abscess, perineal sinus, fistula especially in immunosuppressed individuals. Few cases of tubercular prostate abscess have been reported from India in immunocompromised and immunocompetent individuals (Table 1).

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Table 1 – Reports of tubercular prostate abscess from India.

Studies	Age	Symptoms	Clinical findings	Investigations	Primary focus	Immune status	Treatment
Santosh Kumar et al,2006[8]	52	Fever with chills, LUTS,[a] purulent discharge per urethra	Bilateral epididymoorchitis, boggy prostate, perianal abscess	USG: Hypoechoeic lesion in prostate Cystoscopy: Rectoprostatic fistula and high anal fistula	Pulmonary TB	Immunocompetent	After six weeks of ATT,[b] diverting colostomy, then ATT continued
Nirmal Kumar et al,2006[9]	30	45 days fever	Tender fluctuant nodule in left lobe of prostate	Microscopic hematuria TRUS-Hypoechoeic lesion in posterosuperior aspect of prostate. TRUS guided aspirate shows acid fast bacilli, culture positive for TB	Not found	Immunocompetent	Six months ATT
Suresh et al, 2008[5]	Two cases	–	–	One patient had tubercular abscess with pyocele and coexistent cryptococcal abscess	–	HIV reactive	
Sreejith et al, 2010[10]	30	2 months of fever, renal transplant 5 years back		CT abdomen: Multiple hypodense lesions in liver, spleen, renal allograft and prostate HRCT[c] Thorax-Lungs show military pattern FNAC liver: Acid fast bacilli seen Urine: Acid fast bacilli seen	Pulmonary TB	On immunosuppressives	ATT
Smitha Chandra et al, 2009[11]	–	Fever		Multiple prostate abscess TRUS biopsy-TB	–	Immunocompetent	

[a] LUTS-Lower urinary tract symptoms.
[b] ATT-Antituberculous treatment.
[c] HRCT-High Resolution Computed Tomography.

2. Clinical record

57 year old male patient admitted in the hospital for complaints of fever on and off for the past six months. Also complained of lethargy, dribbling of urine and burning micturition. He was a known ethanolic for the past 30 years. Not a known diabetic, hypertensive. There was no history of tuberculosis. Investigations showed neutrophilic leucocytosis, raised ESR (53mm/hour). Hematogram study showed normocytic normochromic anaemia. Urine culture showed no growth. Blood culture was sterile after seven days of aerobic incubation. Serological tests for typhoid and leptospirosis were negative. X-ray chest showed normal study. USG abdomen revealed enlarged prostate (Grade 3) and prominent left lobe of liver (Fig. 1). Liver function tests show raised direct bilirubin 0.37 g/dl, raised liver enzymes and diminished total protein 5.5 g/dl with albumin 3 g/dl. Serological tests for HIV, Hepatitis B and Hepatitis C were not reactive. Mantoux test was negative.

He was treated empirically with broad spectrum antibiotics. He was also treated for psoriasis vulgaris and adhesive capsulitis of shoulder. Patient continued to have fever. Prostate specific Antigen level was 1.99 ng/ml (within normal limits). CT abdomen showed gross enlargement of prostate with heterogenous density and areas of cystic changes with minimal periprostatic fat stranding consistent with prostatitis with early forming abscess (Grade 3) (Fig. 2) and visualised lung parenchyma showed small thin walled cavity with surrounding centrilobular nodules in posterior basal segment of right lower lobe suggestive of active tuberculous lesion. There were discrete aortocaval lymph nodes of size 1.4 × 1.4 cm. Per rectal examination showed grade 3 prostate with nodular, non-tender left lobe.

USG guided aspiration of the abscess was done and sent for microscopy and culture. Gram stain revealed plenty of pus cells and no organisms seen. Ziehl Nielson stain revealed plenty of curved beaded acid fast bacilli. Early morning midstream urine sample did not show acid fast bacilli. Culture on Lowenstein Jensen medium grew colonies suggestive of *Mycobacterium tuberculosis* after four weeks of incubation which was confirmed by MPT 64 (*M. tuberculosis* protein 64) immunochromatographic test. Antituberculous regimen with two months of isoniazid, rifampicin and ethambutol and seven months of isoniazid and rifampicin was planned. After one month of followup, patient improved symptomatically, did not develop drug induced hepatitis and repeat transrectal USG did not show recollection of abscess.

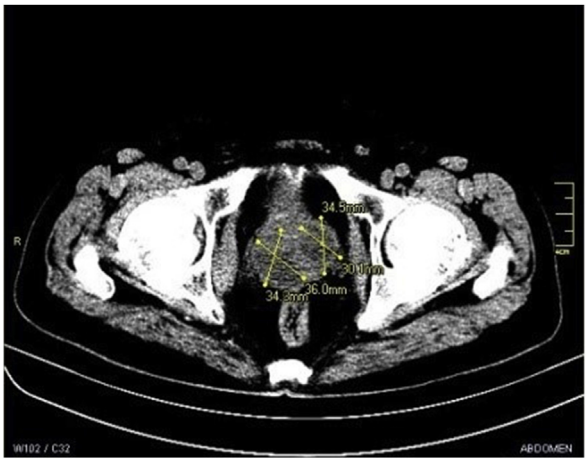

Fig. 2 – CT Abdomen showing grossly enlarged prostate with heterogenous density and areas of cystic changes.

3. Discussion

Prostatic abscess is an infrequent condition in the modern antibiotic era with an incidence of 0.5%–2.5% of all prostatic

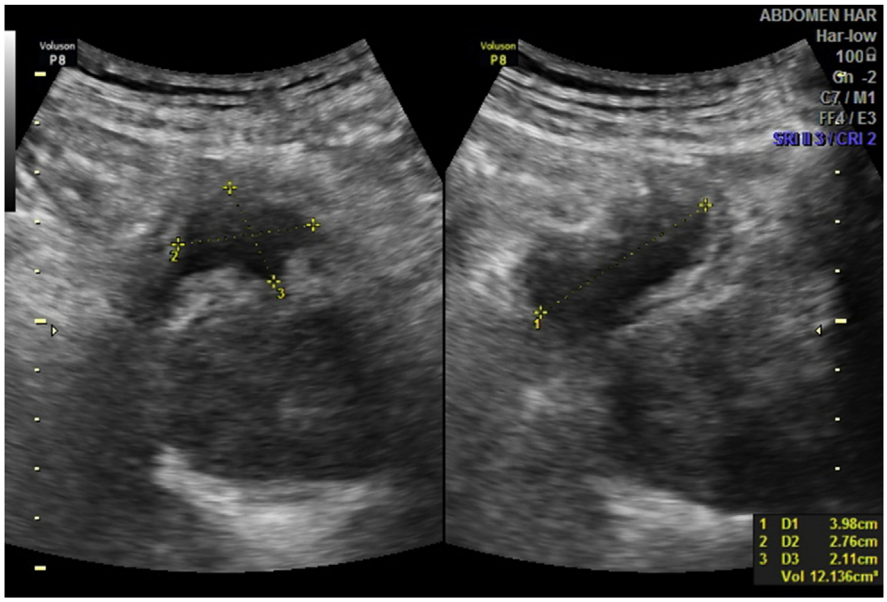

Fig. 1 – USG abdomen showing enlarged prostate (Grade 3).

disease. Prostatic abscess can occur in patients of any age but is mainly found in 5th and 6th decade of life.[3] The clinical diagnosis of prostatic abscess is difficult. This condition usually presents as an irritative voiding symptoms, perineal pain, and fever and occasionally as acute urinary retention. Predisposing factors for development of prostatic abscess are diabetes mellitus, bladder outlet obstruction, indwelling catheter, chronic renal failure, patients on hemodialysis, chronic liver disease and more recently HIV infection.[4]

The microbiology of prostatic abscess hasundergone a complete metamorphosis in the antibiotic era. More recently, various reports have shown that the common organisms causing prostatic abscess are *Escherichia coli* and other enteric gram negative bacilli. However, the prevalence of immunocompromised individuals has increased in the modern era and the potential for uncommon fastidious pathogens, particularly mycobacterial, fungal and anaerobic pathogens, melioidosis,[5,6] in addition to typical gram-negative bacilli, will make the diagnosis of prostatic abscess more complicated. Thus it is important to emphasize that pus culture should be performed routinely for management of prostatic abscess. Urine culture may be negative unless the abscess ruptures into urethra or bladder.

Potential complications due to delayed diagnosis include spontaneous rupture into the urethra, perineum, bladder or rectum and the development of septic shock with a mortality rate of 1%–16%.In immunocompromised settings and countries like India it is imperative to perform drug sensitivity testing for *M. tuberculosis* as MDR (Multi Drug Resistant) strains are on the rise. Existing data shows that the use of TRUS for the diagnosis of prostatic abscess is as sensitive as CT or magnetic resonance imaging.[7] Percutaneous approaches (transrectal and transperineal) to drainage of abscess have come into favor due to their less invasive nature and association with lower morbidity. However, a complete course of antituberculous treatment is the key component in management strategy.

With reduced incidence of prostatic abscess, it is likely that many clinicians may go their entire careers without encountering what was once a fairly common presentation. However, the possibility of severe sequelae of an untreated prostate abscess represent a strong impetus for becoming acquainted with the diagnostic and interventional strategies. Prostatic abscess should be considered as a possible etiology when evaluating for pyrexia of unknown origin in 5th and 6th decades of life. Our patient showed radiological evidence of pulmonary tuberculosis which disseminated to prostate. Also showed evidence of chronic liver disease which could be the predisposing factor for the patient to develop prostate abscess.

Conflicts of interest

All authors have none to declare.

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Case Report

Iatrogenic *Mycobacterium abscessus* infection in a trigger finger

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ABSTRACT

An immunocompetent 63-year-old lady developed *Mycobacterium abscessus* soft tissue infection of the hand following local corticosteroid injection for trigger finger. The patient was successfully treated with repeated radical debridement and prolonged antimicrobial therapy. Atypical mycobacterial infections, including those caused by *M. abscessus*, albeit rare, should be considered in cases of late-onset indolent infection following local injury surgical procedures, and injections. Clinical vigilance, timely diagnosis, combined directed antimicrobial treatment, coupled with adequate surgical debridement are key for successful management.

1. Introduction

Injection of corticosteroid into the flexor tendon sheath is widely accepted as the first-line therapeutic modality for trigger fingers. The exact incidence of postinjection infection is unknown, but it is quite rare.

Mycobacterium abscessus is an acid-fast, rapidly growing nontuberculous mycobacterium. It is considered as the most pathogenic and chemotherapy-resistant mycobacterium of the pathogenic rapidly growing mycobacteria.[1] Though an uncommon cause of human disease, *M. abscessus* may cause pulmonary disease and disseminated infections.[2] Cutaneous and soft tissue infection usually occurs after skin injury following inoculation, minor trauma, or surgery.[3]

M. abscessus hand infections are rare and usually occur in immunocompromised patients and in patients injected with contaminated substances, or through the use of infected needles.[4]

2. Clinical record

A 63-year-old nondiabetic woman, treated with dronedarone and warfarin for paroxysmal atrial fibrillation, and losartan potassium/hydrochlorothiazide for hypertension, was initially hospitalized in another institution nearly five weeks prior to presenting to our department because of a two months' growing swelling and increasing pain in her left palm, which started ten days following local injection of

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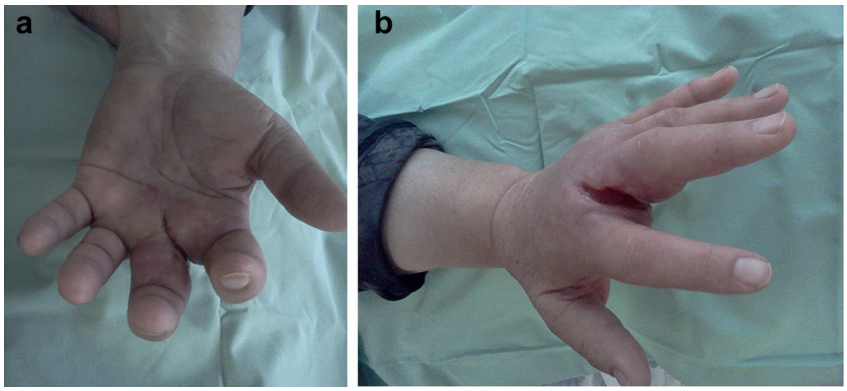

Fig. 1 – (a,b): Erythematous swelling of both palmar and dorsal aspects of the hand. Notice the dehisced wound at the second interdigital web.

corticosteroid for trigger middle finger. Incision and drainage of local fluctuating induration were performed twice and intravenous amoxicillin/clavulanate was initiated. However, her symptoms worsened and she moved to another institution where she underwent a third wound debridement and delayed primary suture. *M. abscessus* was detected by polymerase chain reaction (P.C.R.), and prolonged treatment with oral clarythromycin was recommended. The swelling worsened and spread to the dorsum of the hand, accompanied by pain, stiffness of the fingers and discharge from the wound. She was admitted to our hand surgery unit, and was found to be febrile. She had tender erythematous swelling of both palmar and dorsal aspects of the hand, with maximal tenderness located palmar to the third ray, as well as a discharging dehisced wound extending from the dorsum of the distal third metacarpal into the second interdigital web, and additional minor discharging dorsal sinuses (Fig. 1). There was no clinical evidence for purulent tenosynovitis or arthritis, nor were there signs of ascending lymphangitis. Radiographs showed soft tissue swelling without bone changes. Blood investigation revealed elevated erythrocyte sedimentation rate (50 mm/h), and C-reactive protein was 21.7 mg/L. The patient underwent two surgeries for incision of the fluctuating tissue, drainage, surgical debridement, and irrigation. Tissue samples were obtained, and intravenous amikacin and imipenem, and oral clarithromycin were initiated. Postoperative local wound care and dressings were performed repeatedly. Histological examination revealed granulation tissue with necrotic foci and abundant inflammatory cells. Ziehl–Neelsen stain was negative. Tissue cultures grew non-tuberculous *mycobacteria*, identified by routine microbiologic methods and by PCR as *M. abscessus*. A slow decrease of pain, swelling, and erythema was witnessed within the first two postoperative weeks, accompanied by formation of granulation tissue and, ultimately, successful secondary healing. The patient received vigorous hand therapy; finger mobility has gradually and progressively improved (Fig. 2). The patient was treated for 30 days with intravenous amikacin and imipenem through a peripherally inserted central catheter (P.I.C.C.), followed by oral clarithromycin for two additional months. During two months of follow-up, no relapse of infection was evident clinically, and total active motion of the third finger was 220°, with good grip.

3. Discussion

M. abscessus which was first described by Moore and Frerichs[5] in 1953, is a ubiquitous environmental pathogen that have been isolated also from diverse hospital environments. The

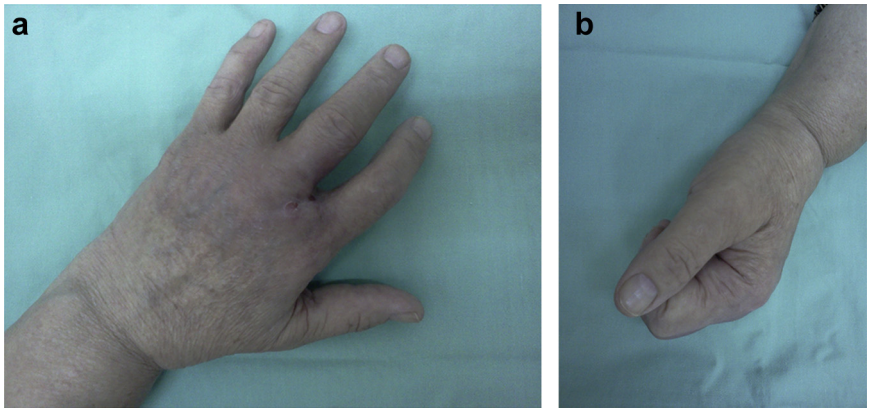

Fig. 2 – (a,b): Complete wound healing by secondary intention, and gradual functional improvement. A flat fist, and subsequently an effective grasp were achieved following hand therapy.

clinical range of infections is broad and includes tender erythematous, violaceous nodules and plaques, cellulites, abscesses, ulcers, osteomyelitis, and draining sinuses with serosanguinous discharge. Clinical signs usually develop within a few weeks to a few months after exposure.[6] *M. abscessus* can grow on standard bacteriologic media, and on mycobacterial solid or broth (liquid) media. They appear as Gram-positive, acid-fast, rods.

Skin and soft tissue infections caused by *M. abscessus* have been described as complications following various invasive procedures, including acupuncture, Mohs micrographic surgery, liposuction, and mesotherapy.[6] None of these reported cases involved the hand.

Mycobacterial infection in our case was circumstantially related to initial local injection. The non-purulent, indolent and persistent course of infection was suggestive, though a direct causation couldn't be decisively confirmed. Furthermore, while initial injection has been done in an office visit, subsequent surgical procedures were undertaken in a sterile setting of an operating theater, further reinforcing the assumption that the initial injection is the probable way of contamination rather than subsequent interventions.

While hand infection caused by *Mycobacterium marinum* is well-known in patients with aquatic or fish exposure,[4] those caused by *M. abscessus* are rare. Galea and Nicklin[7] reported a case of *M. abscessus* infection of the hands in a 55-year-old lady following hand rejuvenation with structural fat grafting. Kang et al[4] reported two cases of *M. abscessus* infection of the hand in otherwise healthy fish handlers. Zenone et al[8] reported a case of finger tenosynovitis associated with CD4+ lymphocytopenia. *M. abscessus* is usually resistant to conventional antituberculous drugs, but generally susceptible to parenteral therapy with amikacin, cefoxitin, and imipenem, and to oral medication with clarithromycin.[3] Extended course of combined antimicrobial therapy is recommended, coupled with repeated surgical excision of necrotic tissue, draining of abscesses, removal of foreign bodies, done consecutively as needed over an extended period of up to several months. The single, most important factor for determining the course and prognosis of *M. abscessus* infection is the underlying immune status of the host.[9] Our patient was not immunocompromised, however, a local immunosuppressive effect induced by corticosteroid instillation is possible.

The paramount importance of using sterile equipment and employing adequate measures in all medical procedures cannot be overemphasized. Timely diagnosis and aggressive, combined treatment may minimize morbidity and improve prognosis. Laboratory personnel should be informed that a mycobacterial infection is suspected, a longer incubation period of samples is required, and specific media have to be used. Atypical mycobacterial infections, albeit rare, should be considered in cases of late-onset skin and soft tissue infection following local injury, surgical procedures, and injections. Such infections tend to have an indolent course, non-healing or dehiscent wounds, and poor response to conventional antibiotic and surgical treatments.

Conflicts of interest

All authors have none to declare.

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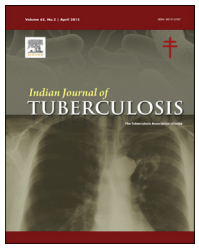

Case Report

Intrathoracic goitre associated with pulmonary tuberculosis

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ABSTRACT

Intrathoracic goitre is an uncommon condition which usually occurs in females in the fifth decade. It can cause compression of several mediastinal structures. A 42-year-old female with goitre since childhood was evaluated for dry cough, occasional wheezing and low grade fever. Imaging showed patchy airspace opacities with cavitation in left lung. Imaging of the neck revealed retrosternal extension of the goitre. Stains and cultures of bronchial aspirate were positive for *Mycobacterium tuberculosis*. A diagnosis of pulmonary tuberculosis with intrathoracic goitre was established, an unusual association.

1. Introduction

Intrathoracic goitre, also known as substernal or retrosternal goitre is seen in 3%–17% of goitres worldwide[1] with an incidence of 0.02%–0.5%.[2] It occurs predominantly in females, generally in the fifth decade of life, with a female: male ratio ranging from 3 or 4:1 to as high as 9:1 in some studies.[3] Although, the most common presentation is growing cervical mass followed by respiratory symptoms due to continuous irritation of the upper airways,[4] up to 20% patients may not have a cervical mass and may be asymptomatic.[3] Compression of mediastinal structures by intrathoracic goitre can cause the patient to present with symptoms like chest pain, venous stasis in neck or arm and dyspnoea.[4] Although, patients with intrathoracic goitre are generally euthyroid, thyrotoxicosis has rarely been reported.[3,5,6] Tracheal compression caused by intrathoracic goitre, can lead to respiratory complications. Pneumonia and atelectasis have been documented in patients with intrathoracic goitre.[7] Bronchial obstruction by intrathoracic goitre leading to atelectasis of middle and lower lobes[8] as well as pulmonary fibrosis and cystic bronchiectasis has also been reported.[9]

The role of thyroid gland in tuberculosis continues to remain a matter of controversy. It has been postulated that clinical hypothyroidism is likely to lower the resistance of the host to tuberculous infection. The increased co-occurrence of goitre and tuberculosis was noted in a large study in children from Calcutta, India.[10] Pulmonary tuberculosis associated with amyloid goitre has been documented in two patients.[11] In another instance, a pregnant female suffering from

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pulmonary tuberculosis along with pleural effusion subsequently developed toxic goitre.[6] However, the occurrence of pulmonary tuberculosis in association with euthyroid intrathoracic goitre, is yet to be documented in the literature.

We report a middle aged lady with goitre since childhood, who presented to us for evaluation of persistent dry cough, occasional wheezing for one year. A low grade fever a fortnight prior to presentation prompted the referral. A diagnosis of pulmonary tuberculosis was established and further investigations revealed that the patient also had retrosternal extension of the goitre.

2. Case report

A 42-year-old HIV-negative housewife, a never smoker, was referred to our Institute for evaluation of persistent dry cough, occasional wheezing, loss of appetite and weight for one year. The cough had gradually increased over the past 5 months. For the last 15 days she also had a low grade fever towards the evening, which prompted the referral. She also had a visible neck swelling since childhood, occasionally associated with palpitations off and on but had not experienced dyspnoea. On presentation, general physical examination revealed a middle aged woman in no acute respiratory distress but febrile. There was no pallor, clubbing, cyanosis or lymphadenopathy. The oxygen saturation at room air was 98%. Diaphragmatic excursion was comparable on both sides. On auscultation, vesicular breath sounds were audible bilaterally with decreased intensity on the left side with prolonged expiration. Bilateral expiratory rhonchi and crepitations were audible also. She also had a left sided neck swelling which moved on deglutition but lower margin could not be delineated. The wheezing and rhonchi were most probably caused by compression of the left main bronchus due to the enlarging intrathoracic goitre. Audible rhonchi on the right side were seemingly due to transmitted sounds since the left main bronchus was involved.

Complete blood counts, ECG, urine analyses and renal as well as hepatic functions were within normal limits. On presentation, patchy airspace opacities were observed in left upper and middle zones on chest X-ray. In addition, loss of volume was also seen along with shift of the mediastinum towards left. A prominent left hilum associated with a raised left hemidiaphragm which obscured the left costophrenic and cardiophrenic angles was also noted (Fig. 1). On presentation, the contrast-enhanced high resolution computed tomography (CECT) of the thorax, demonstrated patchy airspace consolidation associated with necrosis and cavitation along with peribronchial centrilobular nodules in the apical segment of left lower lobe. A large lobulated airspace opacity in apicoposterior segment of left upper lobe with surrounding small patchy fibrotic nodules was also observed (Fig. 2A and B). CT of the neck shows a well-defined lobulated oval peripherally enhancing lesion with central non enhancing necrotic region seen in pretracheal and left paratracheal region causing right sided displacement and partial intrathoracic compression of trachea between T2 to T4 levels in the superior mediastinum (Fig. 3A and B). Sputum stains for acid fast bacilli (AFB) were positive, but cultures for other aerobic organisms and fungi were negative. No induration or erythema was noted with Mantoux test (1 TU) after 48 h. Fiberoptic bronchoscopy, done subsequently, revealed narrowed opening of left main bronchus with presence of mucopurulent secretions. The bronchial aspirate and the post-bronchoscopy sputum were positive for AFB. *Mycobacterium tuberculosis* was also cultured from the bronchial aspirate. Cultures of the bronchial aspirate did not yield any other organism. Multiple endobronchial and transbronchial biopsies revealed granulomas consisting of epithelioid cells and multinucleated giant cells showing intracytoplasmic polarising crystalloid bodies (Schaumann bodies).

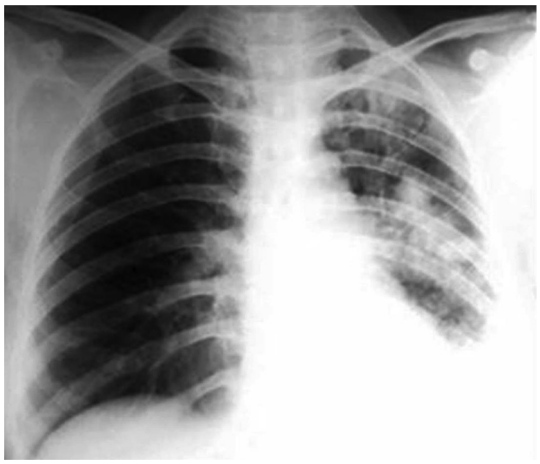

Fig. 1 – Chest X-ray on presentation, showing patchy airspace opacities in left upper and middle zones with loss of volume and shift of the mediastinum towards left. The left costophrenic and cardiophrenic angles were obscured.

Thyroid function tests revealed a euthyroid state. Thyroid scan performed after intravenous administration of 5 mCiTc-99m pertechnetate showed an enlarged left lobe of the thyroid with a hypofunctional area in the lower pole which extended to the lower pole of the right lobe. The left lobe nodule was avascular in nature with a retrosternal extension. Fine needle aspiration cytology from the nodule showed features suggestive of hyperplastic nodular goitre. A diagnosis of goitre with retrosternal extension in euthyroid state along with pulmonary tuberculosis was made.

Once pulmonary tuberculosis was confirmed, the patient was initiated on standard first line antituberculous therapy (ATT) which included rifampicin 450 mg, isoniazid 300 mg, pyrazinamide 1500 mg and ethambutol 800 mg once daily, early in the morning on an empty stomach. After the intensive phase of two months, sputum stains and cultures for *M. tuberculosis* were negative. The patient's symptoms were largely abolished and she expressed a desire to continue ATT at her home town, which was a thousand kilometres away. The patient was advised to consult a thyroid surgeon for her goitre. The patient was then lost to follow up.

3. Discussion

Intrathoracic goitre can be classified into primary which arises from truly ectopic thyroid tissue or secondary that arises from

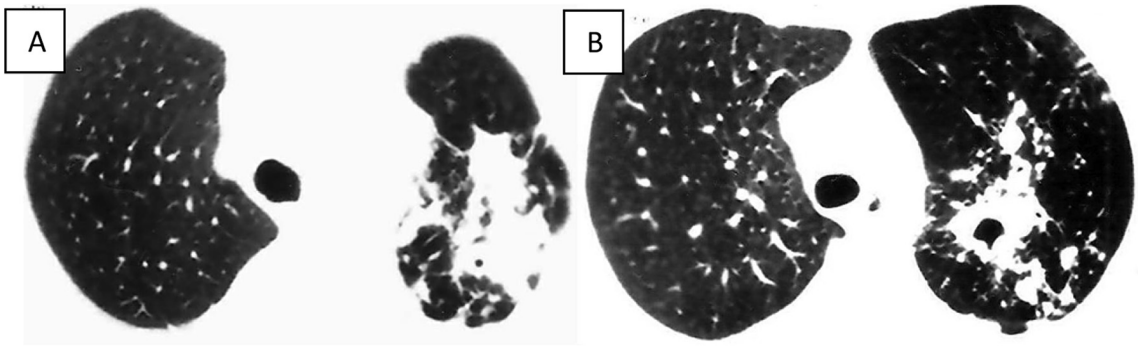

Fig. 2 – A and B: Contrast-enhanced high resolution computed tomography (CECT) of the thorax, showing patchy airspace consolidation associated with necrosis, cavitation. Peri-bronchial centrilobular nodules in the apical segment of left lower lobe along with a large lobulated airspace opacity in apicoposterior segment of left upper lobe with surrounding small patchy fibrotic nodules are also seen.

or has some attachment to cervical thyroid gland.[3] Postural variations in these patients such as lying supine, raising arms, extension of neck or looking to right or left lead to dyspnoea, stridor and facial flushing due to movement of goitrous mass into thoracic inlet.[3]

Intrathoracic goitres usually grow to a size capable of causing compressive symptoms in many years but once symptoms develop they become intolerable in few months.[7] Compression syndromes caused by intrathoracic goitres include cough, asphyxia, tracheomalacia, hypoxia-related right sided congestive heart failure due to tracheal compression. Superior vena cava syndrome, venous thrombosis, portal hypertension, dysphagia, downhill varices, cerebral ischaemia, recurrent laryngeal nerve and phrenic nerve palsy, Horner's syndrome and chylothorax can also occur.[4]

Respiratory symptoms occur due to continuous irritation of the upper airways as a result of compressive nature of the intrathoracic goitre.[4,12] Of the 32 operated patients with intrathoracic goitre, it was observed that tracheal compression led to respiratory complications. Five of these patients had history of pneumonia, four weeks to five months before admission to the hospital, with radiographic evidence of segmental or lobar atelectasis in four of them. The author postulated that narrowing of the trachea is further aggravated by venous congestion since the outflow from the trachea flows into the inferior thyroid vein.[7] A 49-year-old female with intrathoracic goitre, who presented with atelectasis of both middle and right lower lobe due to compression of right bronchus intermedius has also been documented in the literature.[8] Bronchial obstruction due to intrathoracic goitre leading to pulmonary fibrosis with cystic bronchiectasis was described in a 64-year-old female patient.[9] A female patient with intrathoracic goitre with hyperthyroidism, tracheal compression, superior vena cava syndrome, and Horner's syndrome was reported too.[13] Intrathoracic goitre, usually seen in older women, can also occur in young males. A 26-year-old male with 15 year history of dry cough was diagnosed with intrathoracic goitre.[14] Aspiration pneumonia presenting with respiratory failure caused by posterior mediastinal goitre was documented in an 85-year-old male. The patient died due to severe gram negative sepsis.[15]

Association of goitre with pulmonary tuberculosis seems to be rare. In the pre-chemotherapeutic era, pulmonary tuberculosis with pleural effusion was documented in a pregnant female. Subsequently, the patient developed toxic

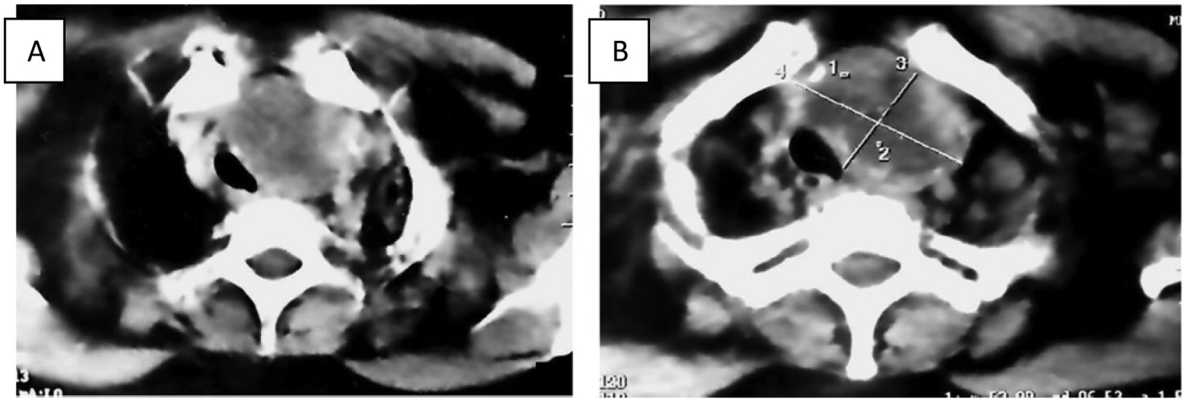

Fig. 3 – A and B: CT of the neck, showing an oval peripherally enhancing lesion with central non enhancing necrotic region in pretracheal and left paratracheal region, causing right sided displacement and partial intrathoracic compression of trachea between T2 to T4 levels in the superior mediastinum.

goitre.[6] A study evaluating 8204 children found that two-thirds of the children had goitre with nearly 60% suffering from tuberculous lymphadenitis. In children with tuberculosis, 49% had goitre. Thyroid enlargement was not seen in 11% of the children. The authors postulated that hypothyroidism predisposes to tuberculosis by retarding the metabolism and lowering the resistance of the host to tuberculosis.[10] Amyloid goitre and associated pulmonary tuberculosis was documented in two patients.[11]

Our patient had a long standing intrathoracic goitre with occasional symptoms and she subsequently developed pulmonary tuberculosis. It is possible that compression of tracheobronchial tree by intrathoracic goitre could conceivably have contributed to the occurrence of pulmonary tuberculosis in our patient. The report is to highlight the very uncommon nature of the association.

Conflicts of interest

All authors have none to declare.

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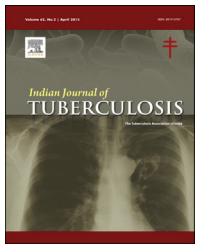

Short Communication

Yield of pulmonary tuberculosis cases by symptoms: Findings from a community survey in Madhya Pradesh, central India

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ABSTRACT

A cross-sectional tuberculosis prevalence survey was undertaken in Jabalpur district, Madhya Pradesh, central India. All individuals were questioned for chest symptoms. Sputum samples were collected and examined for microscopy and culture. Overall prevalence of sputum positive pulmonary tuberculosis was found to be 255.3 per 100,000 population. Cough, with or without other symptoms, was present in 75.5% individuals and yielded 88.2% of the detected pulmonary tuberculosis cases. Elicitation of a previous history of treatment yielded 5.9%, and chest pain 4.5% cases. History of fever alone yielded no cases. The findings suggest that a history of fever alone may be safely excluded from the list of symptoms to be elicited in future TB prevalence surveys in India.

1. Introduction

The prevalence of tuberculosis (TB) disease in a population is estimated by undertaking community based surveys. Though disease prevalence surveys are costly and laborious, they give an unbiased measure of the TB burden at the community level and are justified to be conducted periodically in high-burden countries where many cases and deaths are missed by the routine surveillance systems.[1] However different screening methods, namely symptom elicitation and/or chest X-ray are employed for the detection of cases. With either method, the disease prevalence has been shown to be underestimated; by one-third with symptom screening alone and about one-fifth with chest X-ray alone.[2] In community surveys, the cost of mobile X-ray units including films is high, and comes with significant operational and logistical challenges. Non-availability of motorable roads in many rural/tribal areas of India is also a major constraint. In comparison, symptom elicitation is relatively inexpensive and provides a

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confirmatory bacteriological diagnosis of pulmonary tuberculosis (PTB) as is linked directly with sputum examination of those individuals in whom symptoms are elicited.

Over the decades, a number of TB disease prevalence surveys conducted in India have used symptom elicitation and/or chest X-ray as screening tools.[3–5] However, the yield of PTB cases by the different symptoms has not been documented, except for in one study conducted in south India and another study conducted in central India amongst tribals.[6,7] The present study provides further information on the yield of cases by the various symptoms.

2. Material and methods

The study was conducted in Jabalpur district of Madhya Pradesh, central India, from January 2009 to January 2010. The required sample size was estimated to be about 90,000 adults aged ≥15 years. A house-to-house census was carried out and all permanent residents were registered.

All individuals aged ≥15 years were questioned for chest symptoms relating to TB. Persons with a previous history of anti-TB treatment were also considered eligible for sputum collection. Two sputum samples were collected from all eligible individuals and examined for Acid Fast Bacilli by smear microscopy and culture. The details of the sputum collection and processing have been described in a previously published report of the survey.[8]

Informed written consent was obtained from all individuals. The institutional ethics committee of the Regional Medical Research Centre for Tribals approved the study.

3. Results

Of the total 99,918 individuals eligible for symptom screening, 95,071 (95.1%) were screened. Sputum was collected from 7404 of the 7916 (93.5%) individuals eligible for sputum examination and 221 individuals were found to be bacteriologically positive. Overall prevalence of sputum positive PTB was found to be 255.3 per 100,000 population. The distribution of sputum positive PTB cases (irrespective of culture result) by the various individual symptoms is given in Table 1. Of the total 7404 symptomatic individuals, 5593 (75.5%) had cough for two weeks or more (with or without other symptoms) and yielded 195 (88.2%) sputum positive PTB cases. There were 996 (13.5%) individuals without a cough but who had chest pain for one month or more, who contributed 10 (4.5%) cases. Two hundred and thirty one (3.1%) individuals had fever for one month or more without cough and chest pain, and no cases were diagnosed from amongst these 231 individuals. A total of 141 (1.9%) individuals were without cough, chest pain and fever but had haemoptysis and yielded three cases. The remaining 13 cases (5.9%) were diagnosed from the 443 (6.0%) individuals with a previous history of anti-TB treatment but without cough, chest pain, fever and haemoptysis. The PTB disease was observed to be significantly higher amongst those having cough and also amongst individuals with chest pain (Table 2).

Table 1 – Distribution of sputum positive PTB cases by symptom status.

Symptoms	Sputum examined		Sputum positive cases	
	No	%	No	%
Cough (C)	5593	75.5	195	88.2
Chest pain (P) (without C)	996	13.5	10	4.5
Fever (F) (without C or P)	231	3.1	0	0.0
Haemoptysis (H) (without C or P or F)	141	1.9	3	1.4
History of treatment (without C or P or F or H)	443	6.0	13	5.9
Total	7404	100.0	221	100.0

4. Discussion

Two screening tools, namely symptom elicitation and chest radiography, are generally used in community based TB disease prevalence surveys. In such surveys, the use of chest radiography as a screening tool is challenging due to the common non-availability of mobile X-ray units. The cost of X-ray films and their processing and the requirement of two independent readers, also make the use of this tool a challenge in such surveys. Symptom elicitation is a relatively simple and inexpensive screening tool. It is also rapid, as well as cost-effective. A study conducted by the National Institute for Research in Tuberculosis, Chennai has shown that in surveys conducted in India about two thirds of cases are picked up by symptom screening alone, and that the total prevalence can be estimated by applying a correction factor of 1.7.[2] In the present study, we used symptom elicitation alone, carried out by trained field workers, as the screening tool for the detection of cases. To ensure quality, a supervisor independently interviewed 10% of the adults previously screened by the field workers for symptoms.

The findings of the present study reconfirm the importance of cough as the predominant symptom of TB disease in screened populations. Cough, with or without other symptoms, was present in 75% of the symptomatic individuals and in 88% of the total PTB cases detected in the survey. Similar findings have been reported in other surveys that used symptoms for screening the population.[6,9] The elicitation of a previous history of treatment during symptom inquiry yielded 5.9% cases in the present study. Chest pain was the next most common symptom being present in 996 (13.5%) of symptomatic individuals, and contributing 4.5% of the total cases detected. In this study, the elicitation of either of the two symptoms of cough and chest pain, and/or a history of previous treatment, led to the identification of 95% of the total symptomatic individuals and detection of almost 99% of the total smear positive PTB cases detected in the survey. The contribution of a history of fever alone (without cough and chest pain) in identifying symptomatic individuals was negligible (3.1%) and yielded no sputum positive cases. Similar findings have also been reported by other workers.[6,7] This suggests that a history of fever alone may be safely excluded from the symptoms to be elicited in future community surveys, without any appreciable impact on the number of symptomatics and PTB cases detected. The workload and the

Table 2 – Association of PTB with symptoms.

Only one symptom		Total	Non-TB	TB		OR (95% CI)	P-value
				No	%		
Cough	Yes	2082	2040	42	19	1.69 (1.2–2.4)	0.002
	No	5322	5143	179	81		
Chest pain	Yes	625	619	6	3	3.38 (1.5–7.6)	0.001
	No	6779	6564	215	97		
Fever	Yes	214	214	0	–	–	
	No	7190	6969	221	100		
Haemoptysis	Yes	124	122	2	1	1.89 (0.5–7.7)	0.365
	No	7280	7061	219	99		
History of treatment	Yes	443	430	13	6	1.02 (0.6–1.8)	0.948
	No	6961	6753	208	94		

cost involved in collection and processing of sputum samples can also be reduced as a result.

5. Conclusion

The present study re-confirms history of cough as the predominant symptom to be elicited during the screening of a population for TB disease prevalence surveys in India. The findings also suggest that a history of fever alone may be safely excluded from the symptom screening in future community based TB disease prevalence surveys.

Authors' contributions

RVG, BJ, YR and FWD conceived the study; RVG, BJ and YR designed the study protocol; RVG, BJ, YR and BMK actively participated in the field work for data collection and supervision; MM and BMK did data entry, cleaning and analysis; RVG, BJ, YR, MM and FWD drafted the manuscript. All authors read the final draft and provided inputs to finalise the manuscript. RVG is the guarantor of the paper.

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Conflicts of interest

All authors have none to declare.

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DFW is a staff member of the World Health Organization (WHO). The authors alone are responsible for the views expressed in this publication and they do not necessarily represent the decisions or policies of the WHO.

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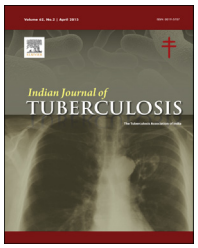

Forum

Profile of NGOs involved in management of MDR TB in Mumbai before rollout of DOTS Plus

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1. Introduction

Prevalence of tuberculosis resistant to at least rifampicin and isoniazid (multi-drug resistant tuberculosis – MDR TB) in Mumbai is known to be higher than the national prevalence.[1]

Diagnostic facilities for MDR TB and Cat IV regimen for treatment of MDR TB were made available in Mumbai in 2012. Before these services were made available, local NGOs played a key role in making expensive long duration second line anti-tuberculosis treatment accessible to the patients from Mumbai. This paper describes the NGOs that were involved in management of MDR TB and services provided by them just before DOTS Plus became universally available in Mumbai.

2. Methods

In the absence of a comprehensive list of NGOs in Mumbai and Thane, a list of 61 NGOs reportedly working with TB patients from Mumbai and Thane Districts was compiled from a listing published by an NGO, personal communication with chest physicians and internet searches. Out of these 61 NGOs, only 46 could be contacted, and only 18 NGOs from those contacted, were found to have supported MDR TB treatment. Sample for the present study consisted of 11 of the 18 NGOs that provided MDR TB treatment and agreed to participate in the study. Of these, ten NGOs were located in Mumbai and one in the adjoining rural Thane district.

In the course of preliminary investigation, it was observed that, clinicians associated with NGOs that did not provide MDR TB treatment, often put patients in touch with pharmaceutical representatives who facilitated patients' access to medicines at subsidised costs. One such medical practitioner (who was associated with an NGO that did not provide MDR TB treatment) was included to represent this group. For the purpose of the study this individual medical practitioner is included in the term 'NGOs'.

The information on services provided by these 12 NGOs was obtained from interviews with administrators or heads (n = 11), clinicians (n = 5), staff or volunteers who dispensed medicines (n = 4) and chest physicians who referred patients to the NGOs (n = 6). Since the NGOs included in the sample functioned with limited staff/volunteers, those available at the clinic at the time of data collection were interviewed for the study. Interviews gathered information on services provided by the NGO, procedures followed on suspicion or before initiating treatment for MDR TB, and role played by clinicians in management of treatment. This information could not be verified with records due to patient confidentiality. Data were collected after seeking permissions from the administrative heads and informed consent from each respondent.

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Additionally, Lists of drugs provided by and patient records for the previous three years were obtained from three NGOs each and were analysed to gain an insight into the NGOs' management of MDR TB.

The study was approved by the institutional ethics committee of The Maharashtra State Anti-Tuberculosis Association.

2.1. *Limitations of the study*

Non-availability of comprehensive listing and contact details of NGOs engaged in MDR TB care resulted in inclusion of easily accessible NGOs in the sample. The sample may not be representative of the NGOs from Mumbai and Thane. The study was of exploratory nature and had a limited scope of documenting clinical support practices of sample NGOs. Information obtained from the respondents was not verified with patient records to prevent breach of provider-patient confidentiality.

3. Results

3.1. *Profile of the NGOs*

NGOs included in the sample varied widely in terms of set-up they operated from, services provided, geographical area covered, number of patients supported and criteria for acceptance of patients into the MDR TB treatment support programme. Only three of the 12 NGOs had support staff that actively followed up with registered patients. Two of these organisations relied on volunteers/persons without professional training while in one organisation post-graduate medical students posted with the NGO followed up on patients.

Three-fourth of the initiatives (9/12) were started in response to the need for support expressed by the MDR TB patients. All NGOs focussed on provision of clinical services. Only one initiative specifically provided medicines to patients who required medicines not provided by DOTS Plus or the other NGOs. While all 12 NGOs helped patients acquire medicines at subsidised costs, only three supported diagnosis and provided specialist clinical services. Two of the three NGOs for which list of medicines was available also provided all or some group 5 drugs required for treatment of XDR TB. Analysis of patient records from two NGOs showed 14% (15/104) patients were prescribed group 5 drugs either according to DST results or based on past treatment history.

Other services provided by NGOs included nutritional support (4/12), vocational training (2/12), information and counselling sessions and support group for patients and families (1/12) (Table 1).

Role played by clinicians at NGO clinics too varied. Three of the five clinicians interviewed monitored the patients, one clinician – chest medicine specialist – decided on regimen as well as followed up patients while the fifth one, merely provided counselling and guidance regarding adhering to the treatment. For patients who approached with diagnosis of MDR TB, four of the five medical officers reconfirmed the diagnosis if reports were not 'recent' or if the patients were diagnosed in private sector or if they failed to improve after two months of treatment. Three of the five medical officers interviewed reported modifying the regimen prescribed by other physicians and only one of these three communicated the modification to the original prescribing physician. Four of the five medical officers reported monitoring patients on MDR TB treatment with the NGO clinic.

Two respondents reported instances where quality of care was compromised because of lack of training of/involvement of non-professional staff. Though not common these point towards possibility of adverse effects if appropriately trained staff is not engaged in patient management.

Most of the NGOs included in the sample did not have interaction with RNTCP and only 5/12 were willing for a partnership with the programme in future.

Patient records from two NGOs showed treatment outcome to be non-favourable (failure, death, default) for 50% (4/8) and 61% (24/39) patients. Proportion of patients who defaulted on the treatment was 31% (12/39) for one of the NGOs. Data on sputum conversion was inconsistent hence not included for analysis.

4. Discussion

In India, historically, NGOs have significantly contributed to tuberculosis control.[2] Global as well as national evidence shows that NGOs continue to play an important role even after introduction of DOTS as partners with national programmes or by complementing national programme.[3,4] The role of NGOs has evolved in response to the needs of the patients and the national programme.

Today, with strong national TB control programme, NGOs can play a complementary role capitalising their unique strengths in reaching out to the communities. Involvement of NGOs as PPM partners could benefit in provision of services such as providing psychosocial or nutritional support to patients - that are a low priority at present in the national programme. Evidence from other countries has shown beneficial effect of these on treatment adherence and therefore on favourable treatment outcome among TB patients.[5–7]

At present the RNTCP uses standardised treatment regimen for MDR TB patients. However, as seen from review of patient records from NGOs, a number of patients need drugs outside of the standardised treatment regimen. Individualised treatment with second line drugs based on DST results is known to be associated with higher cure rates.[8–10] Proportion of patients declared 'cured' or those who completed optimal period of treatment was lower than those reported by DOTS Plus pilot sites as well as those reported by a programme supported by an international NGO.[11–13] NGOs could complement the RNTCP by continuing to support patients with atypical drug susceptibility patterns.

NGOs have not had much interaction with programme. At the same time there is mistrust between the NGOs and GOs. If this is addressed, including facilitating training of NGO staff/volunteers as per the programme guidelines, it would be beneficial for the patients and reach the programme to those who are reluctant to approach public sector.

Table 1 – Profile of NGOs included in the study.

Characteristics of NGOs	Number
Type of initiative	**(n = 12)**
Registered NGOs	10
Located in Mumbai	9
Located in Thane District	1
Individual initiatives	2
In the process of registration as a charitable trust	1
Individual medical practitioner	1
Set-up though which the NGO operated	**(n = 12)**
Polyclinic/dedicated buildings that house all facilities under one roof	4[a]
Stand-alone clinic/NGO office	6[a]
Premises of municipal health care facilities	2
Reason for initiating MDR TB treatment support programme	**(n = 12)**[b]
To respond to the felt need of patients	9
In response to need expressed by social workers from public sector health facilities	3
With modification in public sector drug policies funds used to support other high cost treatments became available to support MDR TB treatment	3
Service provided to MDR TB patients	**(n = 12)**
Chest medicine out-patient clinic	3
Support for diagnosis of MDR TB	3
Reimburse – always	2
Reimburse – sometimes	1
Provision of medicines	12
All medicines –for the entire treatment period – free of cost	5
All medicines – for the entire treatment period – at subsidised rates	3
All medicines – for part of treatment period – free of cost	2
Selected medicines – for the entire treatment period – at subsidised rates	1
Link up patients with sources that provide medicines at subsidised costs	1
Catchment area/Geographical coverage	**(n = 12)**
Not restricted	6
Mostly from some areas from Mumbai	3
From Mumbai, other districts and other states	3
Selected communities (Selected slums/ localities adopted by the NGOs)	4
Patients seeking treatment at certain public sector facilities	2
Number of patients per year	**(n = 8)**
Less than 10	3
30	1
90	1
500	1
More than 3000	1
Criteria for selection of patients for MDR TB treatment support	**(n = 12)**[b]
No selection criteria – accept all patients who approach	6
Patients from specific religious community	1
Patients from particular geographical area	2
Patients referred by particular medical practitioners/centres **(public sector)**	1
Needy/very poor	4
Those who do not get support from any other NGO	1
Non-medical staff that interacted with patients[b]	
Volunteers	3
Permanent/long term employed	1
Professionally trained persons (e.g. doctor, nurse, counsellor etc)	1
Relationship with RNTCP	**(n = 12)**
NGO has some interaction with RNTCP	4
NGO is/was a PPM partner with RNTCP	2
Willingness for partnership	5

[a] NGOs also have a clinic/centre located within the communities they serve.
[b] Multiple response.
Source: Interviews with heads of NGOs (N1 to N11) and medical officer (N12).

5. Conclusion

This small exploration shows that though most NGOs cannot provide quality services independently, they could play a complementary role as partners in PPM. A federation of NGOs involved in TB/MDR treatment could consider partnership with programme for more meaningful results.

Conflicts of interest

The authors have none to declare.

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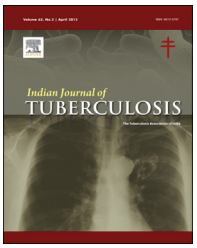
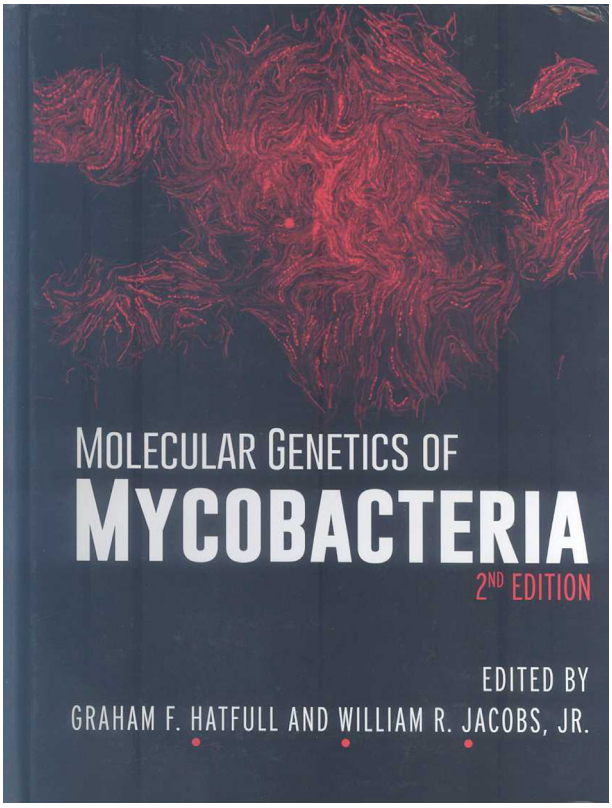


Book Review

Molecular Genetics of Mycobacteria, Graham F. Hatfull, Willium Jacob Jr. (Eds.). 2nd ed. ASM Press, Washington, DC (2014).



The book has a comprehensive collection of interesting topics by leading experts from all over the world in the field of genomics. This multi-author book written excellently, has tried to answer many hidden questions about the gene transfer, gene expression and genetic exchange in mycobacterium. It has also dealt, in detail, with mycobacterium persistence and macrophage survival and factors that play part in genetics of macromolecular biosynthesis. Written under eight sections, the book unveils the metabolism of mycobacterium, drug resistance and genetic strategies for identifying new drug targets, and role of genetic engineering. The effect of oxidative stress, hypoxia and acid stress on *Mycobacterium tuberculosis* is an interesting commentary, raising many more questions in the process. A brilliantly written book, it must find a place in the institutional libraries as a reference book and is strongly recommended for researchers in the field of genomics and proteomics.

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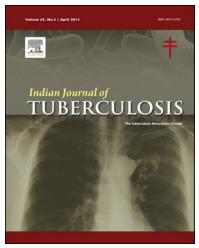

Abstracts

The dynamics of QuantiFERON-TB Gold In-Tube conversion and reversion in a cohort of South African adolescents

Jason R. Andrews; Mark Hatherill; Hassan Mahomed; Willem A. Hanekom; Monica Campo; Thomas R. Hawn; Robin Wood; and Thomas J. Scriba. *American Journal of Respiratory and Critical Care Medicine* 2015; **191(5)**: 584–91. http://dx.doi.org/10.1164/rccm.201409-1704OC.

Rationale: Interferon-γ release assays are used to diagnose tuberculosis infection. In developed countries, high rates of reversion following conversion have been described.

Objectives: To assess QuantiFERON TB Gold In-Tube test (QFT) conversion and reversion dynamics in a tuberculosis-endemic setting.

Methods: Adolescents aged 12–18 years residing near Cape Town were recruited. Tuberculin skin tests (TSTs) and QFTs were performed at baseline and after 2 years of follow up. Half of the participants had TST and QFT performed at additional time points. Participants were observed for incident tuberculosis disease for up to 5 years.

Measurements and main results: Among 5357 participants, 2751 (51.4%) and 2987 (55.8%) had positive QFT and TST results, respectively, at baseline. Annualized QFT and TST conversion risks were 14.0 and 13.0%, respectively, and reversion risks were 5.1 and 4.1%, respectively. Concordance was excellent for conversions ($\kappa = 0.74$), but poor for reversions ($\kappa = 0.12$). Among recent QFT converters, the magnitude of the QFT value was strongly inversely associated with risk of reversion ($P < 0.0001$). When longitudinal QFT data were analyzed in a cross-sectional manner, the annual risk of infection was 7.3%, whereas inclusion of reversions in the analysis showed that the actual risk of infection was 14.0%. Incident tuberculosis was 8-fold higher among QFT reverters than in participants with all negative QFT results (1.47 vs. 0.18 cases/100 person-years, $P = 0.011$).

Conclusions: In this tuberculosis-endemic setting, annual risk of infection was extremely high, whereas QFT and TST conversion concordance was higher and QFT reversion rates were lower than reported in low-burden settings.

Four-month moxifloxacin-based regimens for drug-sensitive tuberculosis

Stephen H. Gillespie; Angela M. Crook; Timothy D. McHugh; Carl M. Mendel; Sarah K. Meredith; Stephen R. Murray; Frances Pappas, M.A.; Patrick P.J. Phillips and Andrew J. Nunn; for the REMoxTB Consortium. N Engl J Med 2014; **371**:1577–87. http://dx.doi.org/10.1056/NEJMoa1407426.

Background: Early-phase and preclinical studies suggest that moxifloxacin-containing regimens could allow for effective 4-month treatment of uncomplicated, smear-positive pulmonary tuberculosis.

Methods: We conducted a randomized, double-blind, placebo-controlled, phase 3 trial to test the non-inferiority of two moxifloxacin-containing regimens as compared with a control regimen. One group of patients received isoniazid, rifampin, pyrazinamide, and ethambutol for 8 weeks, followed by 18 weeks of isoniazid and rifampin (control group). In the second group, we replaced ethambutol with moxifloxacin for 17 weeks, followed by 9 weeks of placebo (isoniazid group), and in the third group, we replaced isoniazid with moxifloxacin for 17 weeks, followed by 9 weeks of placebo (ethambutol group). The primary end point was treatment failure or relapse within 18 months after randomization.

Results: Of the 1931 patients who underwent randomization, in the per-protocol analysis, a favorable outcome was reported in fewer patients in the isoniazid group (85%) and the ethambutol group (80%) than in the control group (92%), for a difference favoring the control group of 6.1 percentage points (97.5% confidence interval [CI], 1.7–10.5) versus the isoniazid group and 11.4 percentage points (97.5% CI, 6.7–16.1) versus the ethambutol group. Results were consistent in the modified intention-to-treat analysis and all sensitivity analyses. The hazard ratios for the time to culture negativity in both solid and liquid mediums for the isoniazid and ethambutol groups, as compared with the control group, ranged from 1.17 to 1.25, indicating a shorter duration, with the lower bounds of the 95% confidence intervals exceeding 1.00 in all cases. There was no significant difference in the incidence of grade 3 or 4 adverse events, with events reported in 127 patients (19%) in the isoniazid group, 111 (17%) in the ethambutol group, and 123 (19%) in the control group.

Conclusions: The two moxifloxacin-containing regimens produced a more rapid initial decline in bacterial load, as compared with the control group. However, non-inferiority for these regimens was not shown, which indicates that shortening treatment to 4 months was not effective in this setting. (Funded by the Global Alliance for TB Drug Development and others; REMoxTB ClinicalTrials.gov number, NCT00864383.)

Sputum induction is a safe procedure to use in prisoners and MGIT is the best culture method to diagnose tuberculosis in prisons: A cohort study

Zulma Vanessa Rueda; Lucelly López; Diana Marín; Lázaro A. Vélez; María Patricia Arbeláez. *International Journal of Infectious*

http://dx.doi.org/10.1016/j.ijtb.2015.04.015

Diseases April 2015; **33**: 82–8. DOI: http://dx.doi.org/10.1016/j.ijid.2015.01.004.

Objectives: To evaluate the concordance and safety of induced sputum (IS) and spontaneous sputum (SS), and estimate concordance and time to detection of *M. tuberculosis* between Lowenstein–Jensen (LJ), thin-layer agar (TLA), and the Mycobacteria Growth Indicator Tube system (MGIT).

Methods: This was a cohort study. Prisoners with pulmonary tuberculosis (PTB) were followed for 2 years. At baseline and every follow-up visit, three sputum samples were taken on consecutive days (one IS and two SS) and adverse events occurring before, during, and 30 min after IS were registered. All sputum samples were stained with auramine and cultured in LJ, TLA (to test resistance), and MGIT.

Results: Five hundred eighty-six IS and 532 SS were performed on 64 PTB patients. Breathlessness (1.6%), cough (1.2%), hemoptysis (0.3%), and cyanosis (0.2%) were the only complications. Concordance between IS and SS was 0.78 (95% confidence interval 0.69–0.87); 11 positive cultures from IS samples were negative in SS, and 11 positive cultures from SS samples were negative in IS. One hundred seventy-eight cultures were positive by any technique: MGIT 95%, LJ 73%, and TLA 57%. Time to detection of *M. tuberculosis* in LJ, TLA, and MGIT was 31, 18, and 11 days, respectively.

Conclusions: The IS procedure is safe in prisons. The MGIT system is better and faster than LJ and TLA in the diagnosis of *M. tuberculosis*.

Optimal duration of anti-TB treatment in patients with diabetes: Nine or six months?

Jann-Yuan Wang; Ming-Chia Lee; Chin-Chung Shu; Chih-Hsin Lee; Li–Na Lee; Kun-Mao Chao; Feng-Yee Chang. *Chest* 2015; **147(2)**:520–8. http://dx.doi.org/10.1378/chest.14-0918.

Background: Diabetes mellitus (DM) increases the risk of TB recurrence. This study investigated whether 9-month anti-TB treatment is associated with a lower risk of TB recurrence within 2 years after complete treatment than 6-month treatment in patients with DM with an emphasis on the impact of directly observed therapy, short course (DOTs).

Methods: Patients with pulmonary but not extrapulmonary TB receiving treatment of 173–277 days between 2002 and 2010 were identified from the National Health Insurance Research Database of Taiwan. Patients with DM were then selected and classified into two groups based on anti-TB treatment duration (9 months vs 6 months). Factors predicting 2-year TB recurrence were explored using Cox regression analysis.

Results: Among 12,688 patients with DM and 43,195 patients without DM, the 2-year TB recurrence rate was 2.20% and 1.38%, respectively ($P < 0.001$). Of the patients with DM, recurrence rate decreased from 3.54% to 1.19% after implementation of DOTs ($P < 0.001$). A total of 4506 (35.5%) were classified into 9-month anti-TB treatment group. Although a 9-month anti-TB treatment was associated with a lower recurrence rate (hazard ratio, 0.76 [95% CI, 0.59–0.97]), the benefit disappeared (hazard ratio, 0.69 [95% CI, 0.43–1.11]) under DOTs. Other predictors of recurrence included older age, male sex, malignancy, earlier TB diagnosis year, culture positivity after 2 months of anti-TB treatment, and anti-TB treatment being ≤80% consistent with standard regimen.

Conclusions: The 2-year TB recurrence rate is higher in a diabetic population in Taiwan and can be reduced by treatment supervision. Extending the anti-TB treatment by 3 months may also decrease the recurrence rate when treatment is not supervised.

Etiology and an integrated management of severe hemoptysis due to pulmonary tuberculosis

Song Yang; Zhuanying Mai; Xiangzhen Zheng; Yueling Qiu. *Journal of Tuberculosis Research* 2015; **3**:11–8. Published Online March 2015 in SciRes. http://www.scirp.org/journal/jtr http://dx.doi.org/10.4236/jtr.2015.31002.

Background: It is very important to enhance the therapeutic effect and prognosis of severe tuberculous hemoptysis after the determining of its etiological cause and the source of bleeding. The etiology and integrated curative effect of severe hemoptysis due to pulmonary tuberculosis among 112 inpatients were analyzed.

Material and methods: The cause was retrospectively analysed. The integrated management effect after the follow-up of mean three years in 112 cases with severe hemoptysis resulting from pulmonary tuberculosis from June 2008 to July 2012 was described.

Results: Active pulmonary tuberculosis ranked the first cause of lower respiratory tract bleeding (32/112, 28.5%), followed by old pulmonary tuberculosis (28/112, 25.0%), tuberculous bronchiectasis (25/112, 22.3%), purified tuberculous cavity (12/112, 10.7%), fungal infection in old pulmonary tuberculosis cavity (9/112, 7.1%), or broncholithiasis (6/112, 5.4%). Almost all sufferers with severe hemoptysis were treated by an integrated management, including psychology, anticoagulants, vasoconstrictor agents. Etiological treatment including anti-tuberculosis and anti-infection was simultaneously or subsequently involved. Sixty-four inpatients with severe hemoptysis who failed to be cured by medical treatment received selective bronchial artery embolization. Four patients received surgical wedge resection, lobectomy or pneumonectomy. The total cure rate added up to 98.2% after mean three years' follow-up. The mortality was 1.8%.

Conclusions: Active pulmonary tuberculosis is still responsible for the severe hemoptysis in the southeast region of China. Severe hemoptysis of pulmonary tuberculosis resulted from stable tuberculosis, tuberculous bronchiectasis, tuberculosis cavity, fungal infection, or broncholithiasis. Better clinical therapeutic effect could be attained by early etiological diagnosis and comprehensive treatment strategy.

Vitamin D deficiency and risk of postpartum tuberculosis among HIV-infected breastfeeding mothers in India

Mave, V.; Chandanwale, A.; Bhosale, R.; Shere, D.; Gupte, N.; Suryavanshi, N.; Kulkarni, V.; Kagal, A.; Bharadwaj, R.; Joshi, S.; Bollinger, R. C.; Gupta, A.; for the SWEN (Six Weeks Extended Nevirapine India) and Byramjee-Jeejeebhoy Medical College Clinical Trials Unit Study team. *The International Journal of Tuberculosis and Lung Disease* 2015; **19(3)**: 302–4.

Some studies have associated low vitamin D levels with the risk of tuberculosis (TB), but its association in human immunodeficiency virus (HIV) infected mothers in a TB-endemic region has not been well studied. We conducted a nested 1:2 case–control study among HIV-infected mothers in western India to evaluate the association between maternal vitamin D levels and the risk of postpartum TB. Vitamin D insufficiency, moderate deficiency and severe deficiency were observed in a high proportion of HIV-infected mothers, but were not associated with the risk of postpartum TB.

Use of rapid point-of-care tests by primary health care providers in India: Findings from a community-based survey

Satyanarayana, S.; Sagili, K.; Chadha, S. S.; Pai, M. *Public Health Action* 2014; **4(4):** 249–51.

In a cross-sectional survey conducted in 45 districts of India, we assessed 1) use of any rapid point-of-care (POC) tests by primary health care providers, and 2) their willingness to use POC tests for tuberculosis (TB) in future. A total of 767 primary health care providers, including private and public sector practitioners, health workers and chemists, were interviewed. A quarter of the primary health care providers reported using POC tests, with pregnancy tests being the most common. Nearly half of the respondents expressed willingness to use POC tests for TB, provided the test was available free or at low cost.

Genetic mutations associated with rifampicin and isoniazid resistance in MDR-TB patients in North-West India

P. Kumar; P. Kumar; V. Balooni; S. Singh. *The International Journal of Tuberculosis and Lung Disease* 2015; **19(4)**: 434–9.

Background: effective tuberculosis (TB) control has been hindered by the emergence of multidrug-resistant TB (MDR-TB).

Objective: To analyse the frequency of drug resistance among presumed cases of drug-resistant TB in the state of Punjab, India, and to determine the frequency of various genetic mutations detected using the line-probe assay (LPA).

Methods: Eight hundred patients with presumptive drug-resistant TB were enrolled under the programmatic management of drug-resistant TB under India's Revised National Tuberculosis Control Programme. Sputum samples from these patients were subjected to smear microscopy and LPA. Clinico-demographic details along with drug resistance patterns and genetic mutations were studied.

Results: After excluding non-eligible samples, 545 samples were analysed, of which 290 (53.2%) showed resistance. Isoniazid and rifampicin (RMP) monoresistance were detected in respectively 9.3% (51/545) and 18% (98/545) of samples, while MDR was present in 25.8% (141/545) of samples. Of the MDR-TB cases, 2.1% (3/141) were treatment-naïve, while 90.8% (128/141) were on retreatment. The most common mutation conferring RMP resistance was S531L.

Conclusion: All patients undergoing retreatment for TB should be tested for drug susceptibility at the initial evaluation. Factors responsible for high MDR-TB and hetero-resistance in Punjab need further studies.

Rifampicin pharmacokinetics in children under the Revised National Tuberculosis Control Programme, India, 2009

Arya, A.Roy; V. Lomash; A. Kapoor; S. Khanna; A. Rangari, G. *The International Journal of Tuberculosis and Lung Disease* 2015; **19(4):** 440–5.

Objective: To evaluate serum levels of rifampicin (RMP) in children with tuberculosis (TB) at doses administered according to India's Revised National Tuberculosis Control Programme (RNTCP) 2009 report.

Method: Prospective, open label, non-randomised single-dose study in 20 children aged 5–12 years.

Setting: The out-patient chest clinic of a tertiary care hospital, New Delhi, India.

Results: The median RMP dose administered was 9.56 mg/kg (range 9–12.64). Peak RMP concentration (C_{max}) attained was 6.24 μg/ml (range 5.44–7.61) at time to C_{max} of 3.5 h (range 3–4). RMP levels were significantly lower at 2, 3 and 4 h in children administered <10 mg/kg than those who received ⩾10 mg/kg ($P < 0.05$). A positive correlation between the RMP dose administered and C_{max} was observed ($r^2 = 0.748$). RMP C_{max} was <8 μg/ml in all patients, a level considered too low for therapeutic efficacy.

Conclusions: Low serum concentrations of RMP were attained in children under the RNTCP 2009 weight band system. Peak RMP levels appear to be lower and the single dose elimination half-life shorter in children than in adults. To optimise treatment outcomes, revisions in RMP dose in children should take into consideration age-related differences in pharmacokinetics.

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*. Published online: March 23, 2015.

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 Jan 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 antituberculosis 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.

Sputum culture conversion as a prognostic marker for end-of-treatment outcome in patients with multidrug-resistant tuberculosis: A secondary analysis of data from two observational cohort studies

Ekaterina V. Kurbatova; J. Peter Cegielski; Christian Lienhardt; Rattanawadee Akksilp; Jaime Bayona; Mercedes C. Becerra; Janice Caoili; Carmen Contreras; Tracy Dalton; Manfred Danilovits; Olga V. Demikhova; Julia Ershova; Victoria M. Gammino; Irina Gelmanova; Charles M. Heilig; Ruwen Jou; Boris Kazennyy; Salmaan Keshavjee; Hee Jin Kim; Kai Kliiman; Charlotte Kvasnovsky; Vaira Leimane; Carole D. Mitnick; Imelda Quelapio; Vija Riekstina; Sarah E. Smith; Thelma Tupasi; Martie van der Walt; Irina A. Vasilyeva; Laura E. Via; Piret Viiklepp; Grigory Volchenkov; Allison Taylor Walker; Melanie Wolfgang; Martin Yagui; Matteo Zignol. *The Lancet Respiratory Medicine* 2015; **3(3)**: 201–9.

Background: Sputum culture conversion is often used as an early microbiological endpoint in phase 2 clinical trials of tuberculosis treatment on the basis of its assumed predictive value for end-of-treatment outcome, particularly in patients with drug-susceptible tuberculosis. We aimed to assess the validity of sputum culture conversion on solid media at varying time points, and the time to conversion, as prognostic markers for end-of-treatment outcome in patients with multidrug-resistant (MDR) tuberculosis.

Methods: We analysed data from two large cohort studies of patients with MDR tuberculosis. We defined sputum culture conversion as two or more consecutive negative cultures from sputum samples obtained at least 30 days apart. To estimate the association of 2 month and 6 month conversion with successful treatment outcome, we calculated odds ratios (ORs) and 95% CIs with random-effects multivariable logistic regression. We calculated predictive values with bivariate random-effects generalised linear mixed modelling.

Findings: We assessed data for 1712 patients who had treatment success, treatment failure, or who died. Among patients with treatment success, median time to sputum culture conversion was significantly shorter than in those who had poor outcomes (2 months [IQR 1–3] *vs* 7 months [3 to ≥24]; log-rank $p < 0.0001$). Furthermore, conversion status at 6 months (adjusted OR 14·07 [95% CI 10.05–19.71]) was significantly associated with treatment success compared with failure or death. Sputum culture conversion status at 2 months was significantly associated with treatment success only in patients who were HIV negative (adjusted OR 4·12 [95% CI 2.25–7.54]) or who had unknown HIV infection (3.59 [1.96–6.58]), but not in those who were HIV positive (0.38 [0.12–1.18]). Thus, the overall association of sputum culture conversion with a successful outcome was substantially greater at 6 months than at 2 months. 2 month conversion had low sensitivity (27.3% [95% confidence limit 16.6–41.4]) and high specificity (89.8% [82.3–94.4]) for prediction of treatment success. Conversely, 6 month sputum culture conversion status had high sensitivity (91.8% [85.9–95.4]), but moderate specificity (57.8% [42.5–71.6]). The maximum combined sensitivity and specificity for sputum culture conversion was reached between month 6 and month 10 of treatment.

Interpretation: Time to sputum culture conversion, conversion status at 6 months, and conversion status at 2 months in patients without known HIV infection can be considered as proxy markers of end-of-treatment outcome in patients with MDR tuberculosis, although the overall association with treatment success is substantially stronger for 6 month than for 2 month conversion status. Investigators should consider these results regarding the validity of sputum culture conversion at various time points as an early predictor of treatment efficacy when designing phase 2 studies before investing substantial resources in large, long-term, phase 3 trials of new treatments for MDR tuberculosis.

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