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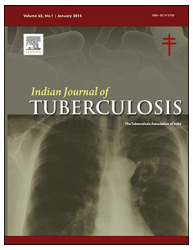

Editorial

India's approach to the standards of TB care

India, the world's second most populous country, accounts for a quarter of the world's annual incidence of TB. Every year, around two million people develop TB in India and 300,000 die of TB.[1] Over 15 million patients have been treated and three million additional lives have been saved by the Revised National TB Control Program (RNTCP) over the last decade.[1] Cure rates have consistently been above 85% and the TB Millennium Development Goals are reachable. However, despite a comprehensive national TB control program guiding states for implementation of TB diagnosis and treatment, there is still a long way to go. The decline in TB incidence has been slow, mortality remains unacceptable high and the emergence of drug-resistant TB has become a major public health concern.

Problem statement: There are many challenges for TB control in India. Prompt, accurate diagnosis and effective treatment of TB are not only essential for good patients care, but they are also the key elements in the public health response to tuberculosis and the cornerstone of any initiative for tuberculosis control. The private sector holds a factual predominance of health care service delivery in India. There is very little information about the TB patient from the private sector treatment, including treatment outcomes. Engaging the private sector effectively is the single most important intervention required for India to achieve the overall goal of universal access to quality TB care.

Need for a local standard: The vision of India's national TB control programme is that the people suffering from TB receive the highest standards of care and support from healthcare providers of their choice. It is spelt out in the National Strategic Plan (2012–17) to extend the umbrella of quality TB care and control to include those provided by the private sector.[1] The need for quality and standards for unmonitored private sector accounts for almost half of the TB care delivered in India with gross challenges as far as quality of diagnosis and treatment is concerned. Thus, it was felt essential to develop and disseminate the standards of TB care that is particularly relevant in India context, acceptable to the medical fraternity in both the public and private sectors in India.

Also, the availability of new diagnostic tools and strategies for early TB diagnosis, emerging evidences on existing regimens and newer regimens, and the need for better patient support strategies including addressing social inclusiveness necessitated the development of standards for TB care in India.

Highlights of International standards for TB care (ISTC): The International standards for tuberculosis care (ISTC) were formulated to develop uniform guidelines for ensuring the delivery of a widely accepted level of care by all health care practitioners in managing TB patients [viz. sputum positive, sputum negative, extrapulmonary, drug resistant forms of TB, TB-human immunodeficiency virus (HIV) co-infection], or those suspected to have tuberculosis. The basic principles of care for persons suffering from TB are the same worldwide: a prompt and accurate diagnosis; advocating the use of standardized treatment regimens supplemented with appropriate treatment support and supervision; monitoring the response to treatment; and carrying out of the essential public health responsibilities. Under ISTC, total 17 standards (viz. diagnosis – 1 to 6; treatment – 7 to 15; public health responsibilities – 16 & 17) have been framed for delivering fixed standard of care.[2]

Need of standards of tuberculosis care in India: India alone has contributed 25% of the globally reported new cases of TB in 2011 and is also the leading nation in accounting for drug-resistant TB (DR-TB).[1] Thus, to develop uniform standards of TB care and to engage private sector which caters to more than 70% of TB patients, the ''central TB division'' has developed standards of TB care in India (STCI).[3] The proposed Indian standards of TB care are not developed with an intention to replace international guidelines, but to ensure the best possible management of TB patients diagnosed in the country. These guidelines have been formulated to develop standardized cost-effective strategies required in the field of diagnostics, treatment and public health-related responsibilities.[2] In addition, it adds standards for social inclusion, which have not been addressed in the ISTC, which in the Indian context has a lot of potential scope in reducing the magnitude of the disease and improving the quality of life of people in the long term.[2]

Therefore, the Indian standards have been designed after taking into account the guidelines of the World Health Organization and ISTC center for disease control. STCI has

Table 1 – Chart showing differences between ISTC and RNTCP guidelines.[5]

ISTC		RNTCP guidelines
Standard 1	Unexplained productive cough of >2–3 weeks should be evaluated for TB	An individual with cough of >2 weeks should be considered a TB suspect
Standard 2	TB suspects should have at least two sputum samples submitted for microscopic examination	TB suspects should have two sputum samples submitted for microscopic examination
Standard 3	EPTB suspects should have a specimen obtained from the suspected site of involvement for microscopy, culture and histopathological examination	EPTB should be diagnosed based on positive tissue culture from an extra-pulmonary site, positive histological findings, consistent radiological finding or strong clinical evidence
Standard 4	CXR findings suggestive of TB merit sputum examination	CXR alone is unreliable for diagnosing TB (implies that sputum examination should be performed for suggestive CXR findings)
Standard 5	Criteria for smear-negative diagnosis: two negative sputum smears, CXR findings consistent with TB and lack of response to broad-spectrum antibiotics: use of fluoroquinolones for empiric treatment should be avoided	Criteria for smear-negative diagnosis: four negative sputum samples, failure of cough to improve on broad-spectrum antibiotics and CXR findings suggestive of TB: fluoroquinolones, rifampicin and streptomycin should never be used for empiric treatment
Standard 6	Describes the work-up and criteria for diagnosis of intra-thoracic TB in children, including sputum or gastric washing evaluation, radiography, history of recent contact with an active TB case, use of TST or IGRA and obtaining tissue or fluid for evaluation in cases of suspected EPTB	Similar work-up recommended to diagnose TB in children, including sputum examination. CXR, history of contact with an active TB case in the last 2 years and use of TST
Standard 7	Providers should assess treatment adherence and address poor adherence when it occurs	A DOT provider should help the patient take medication, thereby ensuring adherence
Standard 8	Defines recommended first-line treatment. 2HRZE + 4HR with dosing conforming to international recommendations: FDCs preferred	Same recommended first-line regimen and dosing standards, although intermittent (every other day or thrice weekly) treatment is preferred: multi-blister combi-packs containing all the drugs are provided by the government
Standard 9	Patient-centred approach recommended, which may include framing of a treatment supporter. DOT and incentives to improve adherence	All standard treatment regimens in RNTCP areas are supposed to be provided by DOT
Standard 10	To monitor response to treatment, two sputum smears should be repeated after completion of the initial 2-month phase of treatment	To monitor response to treatment in smear-positive TB cases, two sputum smears should be repeated at 2 and 4 months and at treatment completion
Standard 11*	DST should be performed for all previously treated patients, patients who remain sputum smear-positive after 3 months of treatment and patients who default, fail or relapse on a course of treatment	DST should be performed for individuals who are close contacts of known MDR-TB patients with a positive sputum smear, those who remain sputum smear-positive after 5 months of treatment and those who default, fail or relapse on a course of treatment with a positive sputum smear (i.e. sputum smear-positive Category 11 patients)
Standard 12*	Patients with suspected or confirmed MDR-TB should be treated initially with a specialised regimen with at least four drugs to which the organism is presumed or known to be susceptible	Patients with suspected MDR-TB should be treated with a standardised regimen of 6 drugs
Standard 13	Written records of anti-tuberculosis treatment should be maintained for all patients	Treatment cards for all patients on treatment should be maintained at RNTCP DOTS centres
Standard 14	HIV testing is recommended universally for all TB patients in high HIV prevalence settings	Routine HIV testing of all newly diagnosed TB patients with unknown HIV status is recommended

Table 1 (*Continued*)

ISTC		RNTCP guidelines
Standard 15	Anti-tuberculosis treatment should not be delayed in HIV patients; all patients with HIV co-infection should be evaluated for initiation of ART if appropriate: cotrimoxazole prophylaxis recommended	All HIV co-infected TB patients are considered seriously ill and should be started on anti-tuberculosis treatment expeditiously: these patients should lie referred to National AIDS Control Programme centres to be considered for initiation on ART and administration of cotrimoxazole prophylaxis
Standard 16*	HIV-infected patients without evidence of active TB should be treated for presumed latent tuberculous infection	No similar recommendation has been made by the RNTCP
Standard 17	Comorbid conditions that may affect anti-tuberculosis treatment outcomes should be assessed and addressed, such as DM, smoking and substance use	Routine screening for DM should be performed for all TB patients with unknown DM status; relevant comorbid conditions such as smoking and pregnancy should be recorded on the treatment card
Standard 18	Close contacts of active TB patients should be evaluated, especially children aged <5 years. HIV-infected contacts, persons with symptoms suggestive of TB and contacts of patients with MDR-TB	All household contacts of individuals with smear-positive TB should be screened for TB symptoms: those with cough should undergo sputum examination
Standard 19	Household contacts aged <5 years or who are HIV-infected without active TB should receive INH chemoprophylaxis	Household contacts <6 years- of age who are asymptomatic should receive INH chemoprophylaxis
Standard 20	Health care facilities that take care of TB patients should have an infection control plan	RNTCP guidelines for infection control in hospital settings recommend administrative controls, environmental controls and personal protective measures
Standard 21	All TB cases must be reported to local public health authorities	All TB cases, including those detected in the private sector, should be mandatorily notified to designated nodal officers in the districts

* Standards for winch the RNTCP guidelines differ[1] from the ISTC.

ISTC = International Standards for Tuberculosis Care; RNTCP = Revised National Tuberculosis Control Programme: TE = tuberculosis; EPTB = extra-pulmonary TB: CXR= chest X-ray; TST = tuberculin skin test: IGRA = mteiferon-gamma release assay: DOT = directly observed treatment: H. ENH = isomazid: R = rifampicin: Z = pyrazrnanii.de: E = ethambiitol. FDC = fixed-dose combination, DST = drag susceptibility testing. MDR-TB = lnultidrug-resistant TE, HIV = human immune deficiency vims; DM = diabetes melhtus: ART = antirefroviral therapy.

proposed 26 standards (viz. diagnosis – 1 to 6; treatment – 7 to 11; public health – 12 to 21; social inclusion – 22 to 26) for effective prevention and control of TB.

Realizing the social aspects and stigma associated with the disease in Indian set-up, standards for social inclusion for TB have been proposed which were not there in ISTC. These include information on TB prevention and care seeking; free and quality services; respect; confidentiality and sensitivity; care and support through social welfare programs; and addressing counselling and other needs.

The Indian standard differs from existing International guidelines in that the standard present what should be done whereas guidelines describe how the action is to be accomplished. There are comprehensive national guidelines from the Central TB division, GOI [www.TBcindia.nic.in] that are regularly reviewed and updated. These standards represent the first what is expected from the Indian healthcare system. It is expected that the standards are clear and usable and will be accessible to all TB providers as a reference.

The Standards for TB care in India (STCI) will assist the healthcare providers in adopting a scientifically approved strategy in the management of all TB patients in the country. The next step logical would be to develop another handbook at the national level using the STCI, as the handbook for using ISTC presents suggestions and guidance, based mainly on country level experiences the delivery of high quality care by all practitioners providing TB services.[4] Therefore, the current national guidelines of India's Revised National Tuberculosis Control Programme (RNTCP) and the recent Standards for TB Care in India (STCI) are largely concordant with the second edition of the ISTC (Table 1).[5]

The patients charter for TB care by the ISTC, which describes the ways in which patients, the community, health providers (both private and public), and governments can work as partners in a positive and open relationship with a view to improving TB care and enhancing the effectiveness of the healthcare process needs to be objectively implemented in day-to-day practice.[6]

The American Thoracic Society, Centers for Disease Control and Prevention and Infectious Diseases Society of America collectively state about the public health implications of prompt diagnosis and effective management of tuberculosis, also empiric multidrug treatment is initiated in almost all situations in which active tuberculosis is suspected. Additional characteristics such as presence of comorbidities, severity of disease and response to treatment influence manage-

ment decisions. Specific recommendations on the use of case management strategies (including directly observed therapy), regimen and dosing selection in adults and children (daily vs intermittent), treatment of tuberculosis in the presence of HIV infection (duration of tuberculosis treatment and timing of initiation of antiretroviral therapy), as well as treatment of extrapulmonary disease (central nervous system, pericardial among other sites) are provided.[7] Another American guideline provides the basis for rational decisions in the diagnostic evaluation of patients with possible LTBI or TB.[8]

One influential approach to the composition of regimens recommends a minimum of five drugs to which the isolate was documented or likely to be susceptible. This approach, to composing what we call an ''aggressive'' regimen, was presented in a 2004 article[9] and used as the foundation for WHO guidelines.

A better understanding of the composition of optimal treatment regimens for multidrug-resistant tuberculosis (MDR-TB) is essential for expanding universal access to effective treatment and for developing new therapies for MDR-TB. The aggressive regimen is a robust predictor of MDR-TB treatment outcome. TB policy makers and program directors should consider this standard as they design and implement regimens for patients with drug-resistant disease. Furthermore, the aggressive regimen should be considered the standard background regimen when designing randomized trials of treatment for drug-resistant TB.[9]

Moreover, INDEX TB guidelines were developed and implemented by the Central TB Division to bridge the gap of early diagnosis and treatment of EPTB. These guidelines serve as a useful tool to the Revised Technical and Operational guidelines of the RNTC programme.[10]

Also, WHO has an implementation plan that is targeted at National Tuberculosis Programme managers and their public and private partners, and all stakeholders were involved in the detection and management of MDR-TB at their country level. It is also relevant for drug procurement managers, technical advisors, specialist clinicians, laboratory technicians, other services providers, relevant government officers, as well as individuals responsible for programme planning, budgeting, resource mobilization and training activities.[11]

Since the inception of Standards of TB care in India guidelines, 2012, there has been a continuous incorporation of the remaining lacunae of the previous other guidelines. Therefore, there is an urgent need for the development of a single guideline, which can serve an ultimate tool for the rapid diagnosis and successful treatment of all forms of Tuberculosis and for achieving the goal of universal access to quality TB care.

To conclude, the Indian standards of TB care have been proposed to emphasize on individual patient care and public health principles of disease control for ultimately reducing not only the suffering but also the economic losses from tuberculosis.

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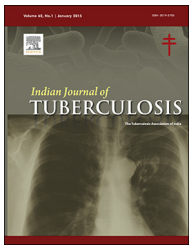

Original Article

The concomitant occurrence of pulmonary tuberculosis with bronchial anthracofibrosis

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ABSTRACT

Background: Bronchial anthracofibrosis (BAF), diagnosed bronchoscopically, is a clinical entity which is now beginning to emerge from obscurity. This is commonly encountered in elderly females with history of long-standing exposure to biomass fuel smoke in poorly ventilated kitchens. As awareness of BAF has increased in recent times, distinct clinicoradiological and bronchoscopic features of the disease have emerged. Diagnosis is achieved by visualisation of bluish-black mucosal hyperpigmentation along with narrowing/distortion of the affected bronchus on fibreoptic bronchoscopy (FOB). BAF was first recognised nearly a decade ago in India, when a 65-year-old female who presented with a middle lobe syndrome (MLS) was diagnosed with concomitant pulmonary tuberculosis and BAF. Pulmonary tuberculosis, seen in up to one-third of patients with BAF, is now considered to be an associated condition rather than a causative agent, as was initially postulated.

Methods: Respiratory symptomatics with a history of biomass fuel smoke exposure underwent high-resolution computed tomography (HRCT) of chest as well as FOB to establish a diagnosis of BAF. In patients who were diagnosed with BAF, an association with tuberculosis was also sought for.

Results: Of the 31 patients diagnosed with BAF in one unit, four had an associated diagnosis of tuberculosis. Cough was the most common presenting symptom seen in all four patients. Imaging revealed consolidation in 3/4 subjects, nodular lesions in one and in another one multifocal narrowing on HRCT, a feature characteristic of BAF. One patient had a diagnosis of MLS. FOB, in all four subjects, visualised anthracotic pigmentation along with narrowing/distortion of the affected bronchi with the left upper lobe bronchus being most commonly affected. Stains and cultures of the bronchial aspirate for *Mycobacterium tuberculosis* were positive in all four patients while GeneXpert performed in three was positive in all. Rifampicin resistance was not detected. One patient had an actively caseating form of endobronchial tuberculosis as evidenced by oedematous, hyperemic mucosa along with whitish cheese-like material affecting the right middle lobe as was seen on FOB.

Conclusion: Once a diagnosis of tuberculosis is established in a patient with long-standing exposure to biomass fuel smoke, invasive procedure required for the diagnosis of BAF is

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usually not considered and the diagnosis would remain confined to pulmonary tuberculosis. This study highlights the need to recognise BAF and to exclude pulmonary tuberculosis in such patients.

1. Introduction

Endobronchial pigmentation along with narrowing of the airways was first described in 1951 by Cohen.[1] He reported eight female patients with perforated tuberculous lymph nodes and narrowing of right middle lobe bronchus. Six of these patients also had anthracotic pigmentation of the affected bronchus. Retrospectively, this would appear to be the first ever description of 'bronchial anthracofibrosis' (BAF), a term coined by Chung et al.,[2] from Korea in 1998. The authors characterised this disease entity with a description of 28 never smokers who had a significant history of wood smoke exposure. A majority of them (20/28) were females with a median age of 64 years. Among these, three-fourths had right middle lobe involvement with active tuberculosis seen in more than 60%. Endobronchial and lymph node tuberculosis were postulated as causative factors in these patients and it was recommended that active tuberculosis must always be ruled out. The authors had even advocated that prompt institution of empirical anti-tuberculous therapy should be considered in all such patients, regardless of bacteriological confirmation. However, evidence implicating long-standing exposure to biomass fuel smoke has emerged as the key aetiological factor in the occurrence of BAF.[3,4]

The disease is characterised by the presence of anthracotic pigmentation commonly seen at the bifurcation of the bronchial tree along with local inflammation and fibrosis leading to bronchial narrowing and distortion.[3] BAF is a bronchoscopic diagnosis and was first documented from India[5] in 2008 in a 65-year-old woman who presented with middle lobe syndrome (MLS) and associated tuberculosis. With increasing awareness, the disease has now been characterised clinico-radiologically, bronchoscopically and has unfolded as a distinct clinical entity. Review of the literature has shown that BAF is commonly associated with tuberculosis, pneumonia, chronic obstructive pulmonary disease and lung cancer.[3] Tuberculosis is now considered as an associated disorder rather than a causative one and can be seen in up to 31% patients with BAF.[3] With tuberculosis being rampant in our country, it is possible that once the diagnosis of tuberculosis is established, the invasive procedure required to establish the diagnosis of BAF may not be done and the diagnosis would remain confined to tuberculosis.

The association of BAF and tuberculosis is yet to receive the attention that it deserves. In light of the above, this study aims to highlight this association seen in patients who had chronic exposure to biomass fuel smoke.

2. Material and methods

Respiratory symptomatics, never smokers, who gave written and informed consent were enrolled. A detailed history of respiratory symptoms and exposure to biomass fuel smoke was recorded. Attempts were also made to understand whether their homes had adequate ventilation or not. These patients underwent chest radiography and high-resolution computed tomography (HRCT) of the thorax. In addition, those patients with a clinical suspicion of tuberculosis had sputum examination for the presence of acid fast bacilli (AFB) and Mantoux test. Fibreoptic bronchoscopy (FOB) was done only in those who again gave a written informed consent just prior to the procedure. The diagnostic criteria adopted for BAF[3,4] were: (1) long-standing history of biomass fuel smoke exposure, (2) on HRCT, the occurrence of multifocal narrowing of involved bronchus when present and (3) visual confirmation on FOB of (a) bluish-black mucosal pigmentation, along with (b) narrowed/distorted bronchus. An associated diagnosis of tuberculosis was based on: (1) bronchial aspirate positive for AFB and/or (2) culture positive for *Mycobacterium tuberculosis* (*M. tuberculosis*) and/or (3) GeneXpert positive for *M. tuberculosis*.

3. Results

Of the 31 patients diagnosed as BAF in one unit, four patients had an associated diagnosis of tuberculosis which has been detailed in Table 1. We had detailed one of the four patients, as the first case of BAF from India who presented with a MLS.[5] All the four elderly patients (three females and one male) were never smokers with a significant history of biomass fuel smoke exposure. None of the four patients had a history of anti-tuberculous therapy in the past. Cough, as a presenting symptom, was seen in all four patients while dyspnoea and constitutional symptoms were documented in 3/4. Chest radiograph (Fig. 1) revealed consolidation in three patients and nodular opacities in one which were confirmed on HRCT of the thorax (Fig. 2A and B). Multifocal narrowing, a feature characteristic of BAF on HRCT, was present in 1/4 patient. Imaging further revealed that right lower lobe was affected in three patients while in two patients each the middle, lingular and right upper lobes were involved. A diagnosis of MLS was established in one patient.[5] Left upper lobe bronchus was involved in 2/4 patients. Sputum stains for AFB were negative in all four patients while Mantoux test was positive in one. Anthracotic pigmentation along with narrowing/distortion of the affected bronchi was visible on FOB (Fig. 3) in all four patients. Stains and cultures of bronchial aspirate were

Table 1 – Characteristics of patients diagnosed with BAF and associated with pulmonary tuberculosis.

	Age/ sex	Symptoms	Biomass exposure	Chest radiograph	HRCT chest	Mantoux test	FOB	TBLB	BA AFB/ GeneXpert
Patient 1	65/F	Dry cough, chest pain × 1 month	Since childhood	PA view: Ill-defined opacity abutting the right cardiac border with loss of cardiac silhouette Lateral view: Wedge-shaped density extending from the hilum anteriorly and inferiorly along with volume loss s/o MLS	Pretracheal calcified lymph nodes Middle lobe consolidation, bronchial wall thickening and nodular infiltrates in the RLL Multifocal stenosis of RML bronchus	Negative	Narrowed but patent RML bronchus with patchy areas of bluish-black mucosal hyperpigmentation	Chronic granulomatous inflammation with epithelioid cell granulomas	Positive for AFB, and culture grew *M. tuberculosis*
Patient 2	80/F	Productive cough, dyspnoea × 3 years Loss of weight and appetite × 4 months	6–7 h/ day × 40 years	PA view: Right mid and lower zone consolidation	Consolidation of RUL and RLL with wedge shaped collapse of lingula	Negative	Bluish-black mucosal hyperpigmentation at the opening of RUL, RLL and LUL bronchus with a narrowed but patent anterior segment of RUL, RLL and lingula	Not done (patient not cooperative)	Positive for AFB, and culture grew *M. tuberculosis* GeneXpert: *M. tuberculosis* detected with no rifampicin resistance
Patient 3	58/F	Productive cough, dyspnoea × 3 years Fever, loss of weight and appetite × 4 months	4–5 h/ day × 20 years	Multifocal areas of consolidation involving the left upper, mid zone and right lower zone	Consolidation in superior segment of LLL and lingula with multiple centrilobular nodules and tree-in-bud opacities Fibrotic patches in superior segment of RLL and LLL with adjacent pleural thickening	Negative	Narrowed/distorted but patent LLL bronchus with areas of bluish-black mucosal hyperpigmentation	Epithelioid granulomas with moderate mononuclear infiltrate suggestive of Koch's	Positive for AFB, and culture grew *M. tuberculosis* GeneXpert: *M. tuberculosis* detected with no rifampicin resistance
Patient 4	66/M	Cough with sputum, dyspnoea × 5 years Fever and loss of weight × 3 months	3–4 h/ day × 20 years Used biomass fuel for cooking and heating the home	Nodular opacities in right upper and lower zones	Nodular parenchymal lesions seen in right upper lobe with plate like atelectasis in right middle lobe	Positive (14 mm)	Narrowed/distorted but patent apicoposterior segment of LUL bronchus as well as bronchus intermedius Oedematous, hyperemic mucosa of the RML covered with a whitish cheese like material suggestive of EBTB	Epithelioid granulomas with foci of necrosis suggestive of Koch's	Positive for AFB, and culture grew *M. tuberculosis* GeneXpert: *M. tuberculosis* detected with no rifampicin resistance

Abbreviations: AFB, acid fast bacilli; EBTB, endobronchial tuberculosis; HRCT, high-resolution computed tomography; LLL, left lower lobe; LUL, left upper lobe; *M. tuberculosis*, *Mycobacterium tuberculosis*; PA view, postero-anterior view; RLL, right lower lobe; RML, right middle lobe; RUL, right upper lobe; TBLB, transbronchial lung biopsy.

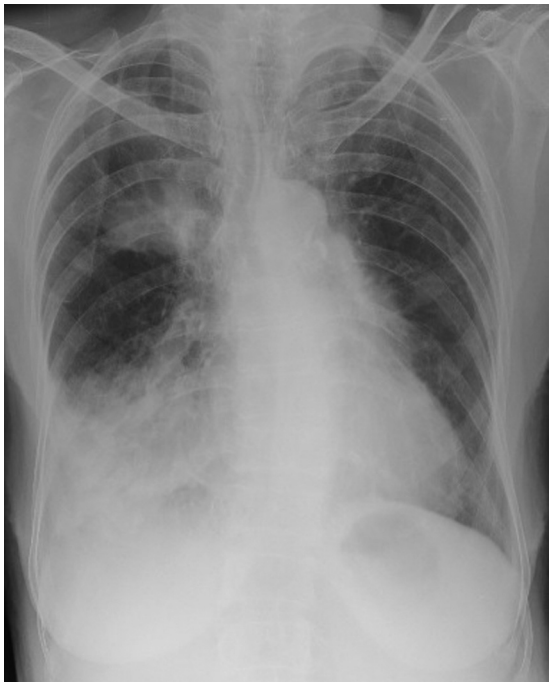

Fig. 1 – Chest radiograph PA view showing right mid and lower zone consolidation.

positive for *M. tuberculosis* in all patients. GeneXpert done in three patients was positive in all while rifampicin resistance was not detected. Transbronchial biopsy done in 3/4 patients was suggestive of granulomatous inflammation consistent with tuberculosis. One patient had an actively caseating form of endobronchial tuberculosis (EBTB)[6] based upon FOB finding of oedematous, hyperemic bronchial mucosa, which was covered with whitish cheese-like material.

4. Discussion

Nearly half the world's population is dependent on biomass fuel smoke for cooking and heating the houses.[4] This dependency on biomass fuel as a source of energy is seen more in the rural areas of developing countries where a large proportion of elderly females spend years cooking in poorly ventilated kitchens. In addition, since a majority of houses lack a separate kitchen, young children and elderly males who stay indoors too are affected.[4] Current evidence suggests biomass fuel smoke as the most important risk factor for occurrence of BAF. The diagnosis of BAF can frequently be missed as BAF can only be confirmed on visualisation of anthracotic pigmentation along with narrowing/distortion of affected bronchus on bronchoscopy. BAF needs to be distinguished from anthracosis where only bluish-black mucosal pigmentation is seen without associated narrowing/distortion of the bronchus.

Although tuberculosis was postulated to be the causative factor for BAF by Chung et al.,[2] it is now documented that BAF is associated with tuberculosis in approximately a third of the patients. Other associated conditions are chronic obstructive pulmonary disease, pneumonia, lung malignancy and rarely interstitial lung disease.[7,8] A study from Canada highlighted that BAF was more likely to occur in immigrants from the Indian subcontinent (50%) as compared to those from other Asian countries (3.7%) and was often associated with pulmonary tuberculosis.[9] It has been postulated that the rather high prevalence of tuberculosis in BAF could be due to: (a) effect of biomass fuel smoke on the activity of pulmonary macrophages, (b) decreased immune response in the elderly, (c) higher prevalence of tuberculosis in elderly subjects and (d) increased sensitivity to *M. tuberculosis* due to silica containing particles.[3] Long-standing exposure to biomass fuel smoke impairs the mucociliary defence mechanism of the respiratory system and reduces the activity of pulmonary macrophage, thus increasing susceptibility to mycobacterial infections. Hwang et al.[9] had documented the presence of refractile, birefringent particles consistent with silica and anthracotic pigment with fibrosis in lung and lymph node specimens of patients with BAF. Aluminium silicates were the most common mineral elements (37.7–97%), and silica was present in a greater concentration in lymph nodes (27.5%) as compared to the lungs (2–7%). Since silicosis has been strongly linked with tuberculosis, this finding may explain the increased risk of tuberculosis with BAF.[3] A meta-analysis from Iran[10] evaluating the association of tuberculosis with BAF showed

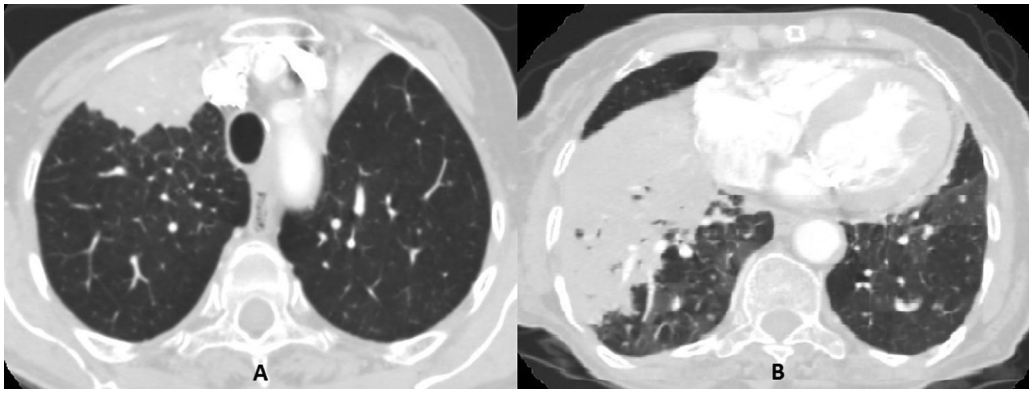

Fig. 2 – (A) High-resolution computed tomography (HRCT) of the thorax (lung window) showing consolidation in the right upper lobe. (B) High-resolution computed tomography (HRCT) of the thorax (lung window) showing consolidation in the right lower lobe.

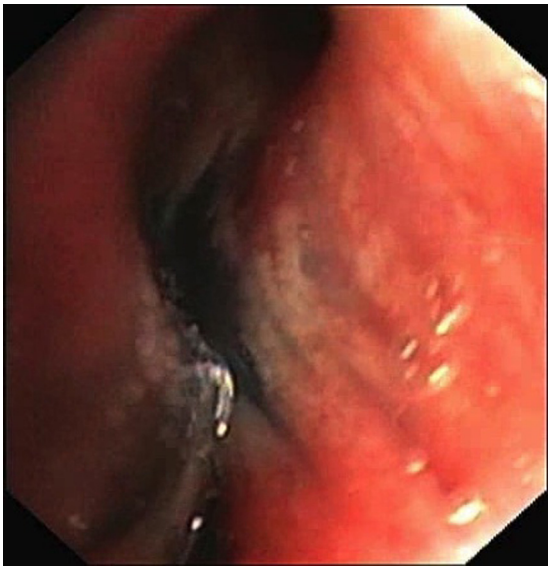

Fig. 3 – Fibreoptic bronchoscopy showing bluish-black mucosal hyperpigmentation along with narrowing and distortion of the right upper lobe bronchus.

that the cumulative incidence of tuberculosis in BAF subjects was 32.3%. The risk of tuberculosis increased in BAF with a cumulated odds ratio of 3.28, which was significantly higher than that of the control group.[10]

All our patients were elderly subjects with significant exposure to biomass fuel smoke. The most common radiological presentation was consolidation. Multifocal bronchial stenosis, a characteristic feature for BAF on HRCT, was present in one patient. In addition, another patient had an actively caseating form of EBTB. Kim et al.[11] documented EBTB in 16% of patients with BAF with the ulcerative variant being most common. Patients with BAF had a higher chance of EBTB (OR 8.88) and it was seen more commonly in the right lung, especially in the right middle lobe bronchus.[11] The authors observed that BAF had a significant association with EBTB. Our patient with EBTB too had lesions in the right middle lobe.

Our study serves as a reminder that BAF is not uncommon in subjects with long-standing exposure to biomass fuel smoke and if present, tuberculosis must be excluded. Unfortunately, for the diagnosis of BAF to be established, there is a need for an invasive procedure like FOB. It is imperative that non-invasive procedures to be developed for the diagnosis of BAF and that grave dangers of exposure to biomass fuel smoke be highlighted. The regulatory authorities must be urged to take steps to curtail the use of biomass fuel.

Conflicts of interest

The authors have none to declare.

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Original Article

Tuberculosis in congregate settings: Policies and practices in various facilities in Mumbai, India

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ABSTRACT

Congregate settings and correctional facilities have high risk of transmission of tuberculosis. They should have capacity to identify and diagnose cases early and initiate prompt treatment to prevent spread to inmates and staff. Appropriate interventions should ensure completion of treatment, documentation and reporting, and prevention of reactivation of successfully treated cases. This requires support from local health authorities. Although international policies and guidelines for infection control in congregate settings are available, there is very little information on how these are practiced in such settings. Our investigation highlights the policies and practices of various congregate facilities in the city of Mumbai.

1. Introduction

Being an airborne infection, the risk of transmission of tuberculosis is high in overcrowded, poorly ventilated settings.[1,2] Malnourished individuals,[3,4] people living with HIV/AIDS, diabetes mellitus,[5,6] elderly persons,[7] and children[8] are at increased risk of infection due to poor immunity. TB prevalence is expected to be high in homes for the aged, orphanages, shelters, prisons, and correctional facilities. Mumbai is one of the most populated cities in the world with more than 60% people living in slums. Rates of TB are high in Mumbai with high proportion of drug-resistant TB (DR TB).[9] Inmates of congregate facilities in Mumbai are likely to be from vulnerable settings and thus may be at significant risk of acquiring TB and also DR TB.

Congregate settings should have the potential to identify and detect cases of tuberculosis early, prevent transmission to others, prevent reactivation of the disease, and liaise with public health authorities for case notification and management.

Numerous international[10] and national guidelines[11] are available for prevention of TB transmission in facilities including health facilities and correctional and congregate settings. These guidelines lay down the principles of prevention of transmission. However, not many countries have legal provisions to ensure the adherence of various facilities to these guidelines.

There are numerous reports on TB in prisons.[12–14] However, in contrast, literature on other congregate settings is scanty. We undertook this study with the objective of assessing the policies, practices, and infrastructure for management of TB in congregate and few correctional facilities.

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2. Methodology

In the absence of a comprehensive directory, a list of 123 facilities was compiled by scanning directories published by various NGOs, through internet search and interviewing key informants from the relevant authorities. Of these, only 70 had valid contact information and were contacted telephonically and briefed about the study. We included 35 consecutively consenting organizations for the study between April and June 2013. These facilities were visited by prior appointment. At the time of the visit, interviews of key informants, who were in charge of administration of the facilities, were conducted using a semi-structured questionnaire. The questions related to the type and number of beneficiaries, admission policies, health screening of staff and inmates, and linkages if any with the public health facilities. TB-specific issues such as periodic screening, management of identified cases, and follow-up were enquired. Wherever possible, a detailed assessment of the facilities was carried out with the help of a checklist to assess the overall hygiene, ventilation, etc. Registers and other documents related to TB were seen.

Data and analysis: Data were entered in Excel and analyzed using SPSS. Frequencies and cross-tabulations were used for the purpose.

The study was approved by the Institutional Ethics Committee of The Foundation for Medical Research: FMR/IEC/TB/01/2012.

2.1. *Observations*

The types of facilities studied and their TB management practices are summarized in Table 1.

Residential capacity of the centers ranged from 6 to 850 with an average of 157 and a median of 60; correctional facilities were overcrowded with 94–248% more inmates than their capacity at the time of the survey. On an average there was one staff member for every 9 inmates (median – 4 inmates; range 1–53 inmates).

Although 28 of the 35 (80%) settings had in-house health facilities, only 2 conducted pre-employment general health screening of the staff; however, none screened specifically for tuberculosis (data not shown); with 15/28 (54%) conducting preadmission screening of the beneficiaries. Centers that did not have in-house healthcare facilities did not have any policy of pre-entry screening of staff or inmates.

Seventy-one percent of settings (25/35) had cases of TB in the last five years. Whether this TB was drug susceptible or resistant could not be ascertained, as this was not documented by the facilities. Also, they did not conduct regular periodic screening of staff and inmates for TB. Contact examination through symptom screening, X-rays, or Tuberculin Skin Test (TST) was not performed by any of the facilities following identification of a case. Facilities referred symptomatics for X-rays, and sputum and tuberculin skin tests sometimes to private but largely to public health facilities.

Nineteen (54%) facilities maintained records of TB cases and 13 (37%) facilities had linkage with the local DOT center for treatment.

Four of the 25 facilities with at least one tuberculosis case in last five years assisted their inmates in getting transfer forms and linking them to the new DOT center after release from the facility; in cases of transfer, all facilities claimed to provide complete health and treatment records to the transferred facility in order to ensure continuation of TB treatment course. Eight shelter homes for children (data not shown) released

Table 1 – Health management practices of the facilities.

		Home for aged	Orphanage	Shelter	Shelter for women	Correctional facility	Others	Total (%)
(a) Type of facilities	Public	0	1	4	0	3	2	10 (29)
	Private	6	5	8	2	1	3	25 (71)
	Total	6	6	12	2	4	5	35
(b) Settings with in-house healthcare facilities	Public	0	1	3	0	3	2	9
	Private	3	4	7	1	1	3	19
	Total	3	5	10	1	4	5	28 (80)
(c) Visiting Physician (full time/weekly)	Public	0	1	1	0	3	2	7
	Private	2	4	4	1	1	2	14
	Total	2	5	5	1	4	4	21 (60)
(d) Availability of TB Records (prior 5 years)	Public	0	1	2	0	1	1	5
	Private	3	4	4	1	1	1	14
	Total	3	5	6	1	2	2	19 (54)
(e) Facilities with TB cases in past 5 years	Public	0	1	2	0	2	2	7
	Private	4	5	4	1	1	3	18
	Total	4	6	6	1	3	5	25 (71)
(f) Practice of Isolation of TB patients among (e) above	Public			1				1
	Private	1	3	4			1	9
	Total	1	3	5	0	0	1	10 (40)
(g) Masks provided to cases among (e) above	Public							0
	Private	1	3	4	1		2	11
	Total	2	6	8	2	0	2	11 (44)

inmates only on completion of the treatment course. Nine of the 25 (36%) facilities reported not having any follow-up services for released inmates who were on treatment.

Only one facility had an airborne infection control (AIC) policy in place. We could not assess most of the facilities for AIC since they did not consent for this. Isolation of active cases from the other residents was practiced by only 10 facilities – space being a major constraint. Cough etiquette and proper sputum collection and disposal procedure were lacking in most facilities; only 11/25 (44%) facilities, which had a case of TB in the last five years, provided masks to the TB patients, but none to the staff attending on them. Two facilities provided special diet to the inmates with tuberculosis. Counseling on various aspects of personal hygiene, nutrition, and cough hygiene was done by 12 centers.

Correctional facilities as mentioned above were overcrowded. Although in-house medical personnel were available, there being no diagnostic facility, inmates had to be transported to the local government hospital. Inadequate arrangement for escorts led to delay in diagnosis. Identified TB cases were segregated in a separate section; however, this section had poor ventilation, which is a risk for cross-transmission. Inmates when released could not be followed up as mechanisms for transfer were not in place and often the inmates provided false addresses.

The study findings were shared and discussed with the City TB Officer, local program managers and administrators of the facilities at three regional stakeholder meetings where considerable interest was generated in developing collaborative linkages between the facilities and the TB program. An action plan was formulated to train the facility staff, set up referral network, and also assess the prevalence of TB in these settings. However, on review a year after the proposed plan, very little progress was observed.

3. Discussion

Our investigation to assess the policies, practices, and infrastructure for TB management in congregate settings and a few correctional facilities highlights various issues that need to be addressed to prevent transmission of TB in these vulnerable facilities.

Congregate settings are places where there is a high concentration of people living together in a shared space. It is well known that overcrowding and prolonged contact contribute greatly to transmission of TB.[15,16] Even in such situations, point of entry and regular periodic screening for TB both for the staff and inmates will minimize transmission.[17] Although 71% of the facilities had TB cases in the last five years, estimation of prevalence of TB in congregate settings is not possible due to lack of diagnostic facilities and absence of a robust referral system. Early detection, prompt regular and adequate treatment along with contact examination of all inmates whenever a case is identified, and appropriate linkages with the public health system for follow-up action will go a long way in prevention of transmission within the facilities and also the community, especially when the inmates are released.[18,19]

Airborne infection control (AIC) plays an important role in preventing transmission.[20] Simple administrative controls such as isolation of the patient wherever there is adequate space or placing the individual near the window, advocating cough etiquette, provision of masks to infectious patients, environmental controls with provision of fans and extractor fans to ensure appropriate air changes in the room, and lastly personal protective masks to staff and other noninfected individuals residing in the same room will go a long way in preventing transmission. Both international and national guidelines are available for AIC in these settings,[10,11] and they need to be disseminated and implemented at the earliest.

The Revised National TB Control Program (RNTCP) in India plans to provide universal access to TB care and should comprehensively include these high-risk settings in their operational plans. Standard operating protocols need to be developed for comprehensive TB detection, care, and follow-up of patients in these settings – with well defined roles and responsibilities of congregate settings and the TB program. The TB program should assist the congregate settings on an urgent basis in training the staff, early diagnosis and treatment of detected cases, organizing transfer of patients to other centers or their homes, and in documentation. Preadmission screening for staff and beneficiaries, identifying suspected cases of tuberculosis and other conditions such as diabetes, HIV infection, and substance abuse with referrals for early diagnosis and treatment and strategies for prevention of transmission to other inmates, organizing contact examination, and institution of airborne infection control measures would be the responsibility of the congregate settings. This model of TB prevention and control would assist in preventing outbreaks of tuberculosis and other airborne infections among staff, inmates, and the surrounding community.[21] Effective implementation of these recommendations would require formulation of regulations, which could be done at the local/regional government level as practiced in some countries.[22,23] The lack of adherence to norms should be viewed as a threat to public health and dealt with accordingly.

Authors' contribution

YD and NF designed the study, YD designed the tools, and YD and NF wrote the manuscript.

Conflicts of interest

The authors have none to declare.

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Original Article

Health-related quality of life among tuberculosis patients under Revised National Tuberculosis Control Programme in rural and urban Puducherry

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ABSTRACT

Background: Globally, tuberculosis (TB) continues to be the major public health problem. Limited research is carried out on the impact of the disease on health-related quality of life (HR-QoL). The study aims to assess the HR-QoL among TB patients during and after Directly Observed Treatment Short-course (DOTS) therapy and to compare the HR-QoL of these patients with matched neighbourhood controls.

Methodology: A community-based longitudinal study was conducted in Ariyankuppam and Bahour communes of Puducherry from January 2014 to April 2015. 92 TB patients registered for DOTS therapy during January–June 2014 were interviewed in their DOTS centres during first visit using the SF-36 questionnaire to assess their HR-QoL. During the second visit, 9 TB patients were lost to follow-up; therefore, a total of 83 patients were interviewed in their houses and, simultaneously, 83 matched neighbourhood controls were interviewed. Non-parametric tests were used to compare the HR-QoL scores. p value <0.05 was considered as statistically significant.

Results: The mean HR-QoL scores had improved among TB patients upon completion of DOTS (80.8 ± 20.3), when compared to HR-QoL scores (48.3 ± 30) during treatment with significant difference. The HR-QoL scores of TB patients after DOTS completion (80.8 ± 20.3) had improved to levels comparable to that of non-TB controls (77.5 ± 29.1) without significant difference.

Conclusion: HR-QoL of patients suffering from TB was low. However, the study provides evidence that DOTS treatment offers a demonstrable improvement of HR-QoL among TB patients almost to the level of general population. The findings can be used in advocating the effectiveness of DOTS in TB control efforts.

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1. Introduction

Tuberculosis (TB) is an infectious disease caused by *Mycobacterium tuberculosis*, predominantly transmitted by infectious droplet nuclei.[1] The causative organism of TB was discovered more than 100 years back, and highly effective drugs and vaccine are available making TB a preventable and curable disease. Despite these advancements in medical managements and techniques, TB continues to be a one of the major public health problems globally.[1]

Each year, there are around 9 million new cases of TB, and close to 2 million people die from the disease.[2] Directly Observed Treatment Short-course (DOTS) is one of the most cost-effective measures in controlling the TB. With the recent development of effective TB management strategies, the focus has shifted from the mortality prevention to morbidity reduction. This decline in disease rates has been attributed to changes in the non-specific determinants of the disease such as improvement of standard of living and quality of life of the people.[3]

The Revised National Tuberculosis Control Programme (RNTCP) in India applies the DOTS strategy in the diagnosis and treatment of TB disease. The programme routinely focuses on bacteriological markers of response and on outcomes such as cure, mortality and treatment default/failure. However, there are various aspects that may lead to a poor health-related quality of life (HR-QoL). TB patients distinguish themselves to be at risk of stigma-related social and economic consequences, making the individual feel rejected and isolated from their families and friends.[4] Besides the sufferings from the disease, the treatment itself may have a role in affecting the HR-QoL, which includes prolonged TB treatment (at least 6 months) with multiple drugs that can lead to adverse reactions in TB patients though it is temporary, compared to the benefits.[5] Finally, there is a lack of knowledge regarding the disease process and its treatment among rural and urban slum populations affected with TB, which may contribute to feelings of powerlessness and anxiety.[6]

Societies have started to recognize health as a basic human right and are now demanding a better HR-QoL. Measuring a disease's impact on the HR-QoL of the patient is an important component in making policy decisions. Therefore, stakeholders all over the world are now increasingly concerned about improving the HR-QoL of their citizens by providing primary healthcare services to the people thereby enhancing the physical, mental and social well-being of the population to ensure good HR-QoL of their citizens.

With these vacuities in literature, we conducted a longitudinal study in the community to assess the HR-QoL during and after DOTS treatment among TB patients under RNTCP compared to a non-TB control group in Puducherry using the SF-36 tool.

2. Methodology

Ethical Committee approval from Institutional Human Ethical Committee and funding approval from state TB control society were taken before commencing the study. Permission was obtained from The Mission Director, Puducherry State Health Mission and from the Tuberculosis Programme Manager, Chest Clinic – Puducherry to access the details of the registered cases of TB from the TB register at Chest Clinic, CHCs and PHCs covered under our study area.

2.1. Study setting

The study was conducted in Ariyankuppam and Bahour Commune Panchayats of Puducherry, situated in southern part of India. The study area was covered by 4 DMCs cum DOTS centre (1 CHC/3 PHC) and 3 DOTS centres (3 PHCs).

2.2. Study participants

2.2.1. Case

The study included all willing pulmonary and extra-pulmonary TB patients aged above 18 years registered for DOTS therapy in the study area during January 2014–June 2014.

2.2.2. Controls

Age, sex and co-morbidity matched non-tuberculous individuals from the patients' neighbourhoods were included as controls to document the HR-QoL among the general population in the study area. If the TB patient has more than one co-morbidity, any one co-morbidity was matched for the controls.

2.3. Study tool

The investigator interviewed the TB patients and non-TB controls in local language using a pre-designed proforma.

2.3.1. Health-related quality of life assessment questionnaire and its scoring

HR-QoL among TB patients and non-TB controls was assessed using SF-36 questionnaire.[7,8]

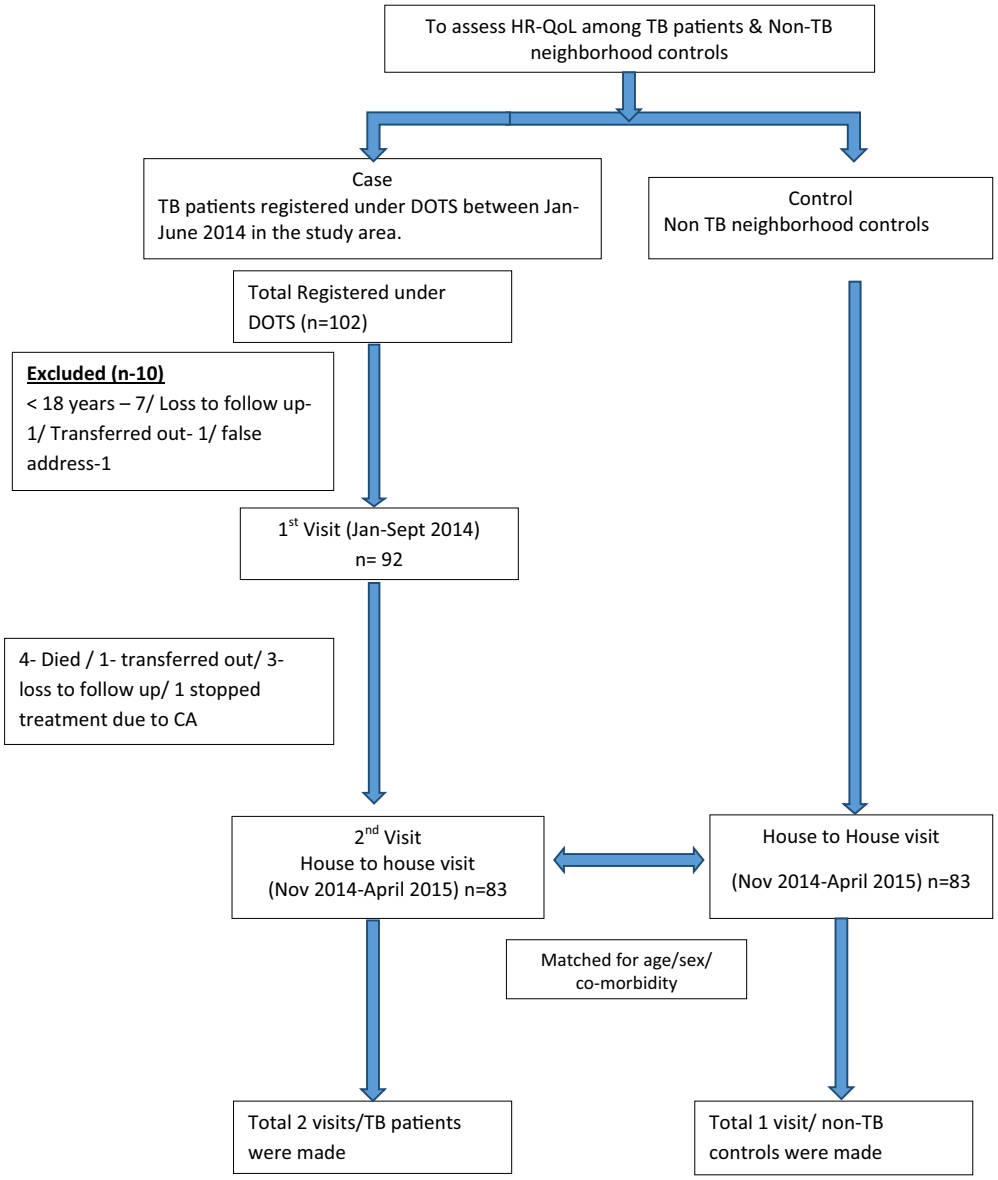
It contains 8 categories to assess the diverse concepts of health including physical functioning (PF, 10 items), energy/vitality (VT, four items), role physical (RP, four items), social functioning (SF, two items), bodily pain (BP, two items), role emotional (RE, three items), general health (GH, five items) and mental health (MH, five items).

Responses to each of the SF-36 items are scored and summed according to a standardized scoring protocol, and expressed as a score on a 0–100 scale for each of the eight health concepts.[7,8] Higher scores represent better self-perceived health.

The Tamil language translation of SF-36 questionnaire involves multiple independent forward translations by native speakers, reconciliation of the translation into one form and back translation of this Tamil SF-36 questionnaire into English to check the originality of the translation.

2.4. Study design

The present study was a prospective longitudinal study.



2.5. *Data collection procedure*

The investigator interviewed the TB patients and non-TB controls in local language using a pre-designed proforma. During January 2014 to September 2014, TB patients who were registered in our study area were contacted personally by the principle investigator after the DOTS registration in their respective centres and were invited to participate in the study after explaining the purpose and scope of the study. Those who gave consent to participate were assessed by the study tools and the outcomes were measured soon after their DOTS registration while the patient came to the PHC/CHC to collect their drugs. Out of 102 TB patients registered for DOTS, 1 patient was transferred out, 1 patient could not be contacted as she is doing her college outside the study area, 1 patient had wrong contact address and 7 patients were less than 18 years. Totally, 92 patients were interviewed during the first visit.

The second visit was conducted after three completing months of DOTS treatment for both categories I and II TB patients. From November 2014 to April 2015, after completion of DOTS therapy, out of 92 patients, 83 TB patients were followed-up by house visits. Nine patients out of these 92 were lost to follow-up (not completed their treatment) due to the following reasons: 4 patients died, 1 patient was transferred to Madurai railway hospital after the completion of his intensive phase, 1 patient stopped treatment as she was diagnosed to have endometrial cancer and on radiotherapy, 1 patient was loss to follow-up after 3 consecutive visits due to change of address and 2 TB patients defaulted from treatment due to shift of their work. Totally, 83 TB patients were contacted through phone, prior to the visit to fix a mutually convenient time for the second visit, and then house visit was done. The SF-36 questionnaire measuring HR-QoL was administered again and the outcomes were measured.

Simultaneously, 83 matched controls with respect to age, sex and co-morbidities were selected from the neighbourhoods of the TB patients. The same set of questionnaire was administered to elicit their demographic profile and HR-QoL among the control group.

Besides principle investigator, additional data collectors for the data collection procedure were recruited in this study. Prior to the start of our study, the additional data collectors were explained about the purpose of the study and adequately trained for the data collection procedures. Written, informed consents were obtained from both TB patients and controls. Privacy and confidentiality were maintained throughout the study period.

2.6. *Statistical analysis*

The data were entered in Microsoft Excel 2010[9] and analyzed using Epi Info™ 7.1.5[10] statistical package. To compare the HR-QoL scores among TB patients during DOTS treatment and after their completion, non-parametric test – Wilcoxon signed rank test was used. To compare the HR-QoL scores among TB patients and non-TB controls, non-parametric test – Mann–Whitney test was used. To avoid variability that influences the results, 9 lost to follow-up TB patients' details were excluded for all the analysis. p value <0.05 was considered as statistically significant for all the above calculations.

3. Results

In the present study, 92 TB patients and 83 neighbourhood controls matched for age, sex and co-morbidities were included. The mean age of TB patients and controls were 45.7 ± 13.9 and 45.2 ± 13.6, respectively. Marital status and literacy status in both groups were similar.

It was observed that out of 92 TB patients, 30 (32.6%) of them were unemployed, whereas 14 (16.9%) from the non-TB control group were unemployed with significant difference ($p = 0.001$). Significant difference was found in terms of mean individual salary and socio-economic status among TB patients and non-TB control group with p values 0.04 and 0.001, respectively.

The mean interval between TB registration and 1st visit for both categories I and II TB patients was 7 (2) days. The mean duration of 2nd visit after DOTS completion for category I patients was 3.0 (0.1) months and, for category II patients, it was 3.3 (0.1) months, whereas MDR patients are still on treatment.

HR-QoL was compared between TB patients and non-TB patients using SF-36 questionnaire. Table 1 shows the comparison of TB patients during their DOTS treatment and non-TB controls and the finding suggests that the TB patients during their DOTS treatment (48.3 ± 30.0) had poor HR-QoL on all dimensions than the non-TB controls (77.5 ± 29.1) with significant differences ($p < 0.001$). The mean differences found between these two groups ranges from 15 to 40.

Table 2 shows the comparison of HR-QoL of TB patients during and after completion of DOTS treatment. Overall mean scores of HR-QoL had improved on all dimensions among TB patients upon completion of DOTS (80.8 ± 20.3), when compared with HR-QoL measured during their DOTS treatment (48.3 ± 30) with significant difference ($p < 0.001$).

The total mean score of the HR-QoL was 80.8 (20.3) and 77.5 (26.9) for TB patients and non-TB controls, respectively. Overall, the mean score of HR-QoL on all dimensions among TB patients after their DOTS completion and a mean score of HR-QoL among non-TB controls was similar with no significant difference ($p > 0.05$) (Table 3).

4. Discussion

In India, there is still a paucity of community-based studies on assessing HR-QoL among TB patients using the SF-36 score.

Poor HR-QoL is likely to be an important factor in TB treatment adherence, especially in the intensive phase of treatment for directly observed treatment. SF-36 questionnaire contains 8 domains; each domain represents a specific facet of the HR-QoL of TB patients. In the present study, the overall mean score at the onset of DOTS treatment was below 50%, which highlights that the TB patients had poor HR-QoL during the treatment course. During the initial assessment, among all the SF-36 domains, 'energy' has least mean score (39.6 ± 25.5) followed by 'general health' (44.2 ± 24.1) and 'emotional well being' (44.4 ± 24.7). However, after completion of DOTS treatment, TB patients showed improvements in HR-QoL with significant differences ($p < 0.001$), which indicates positive impact on TB regimens over the HR-QoL. However, the

Table 1 – Comparison of SF-36 scores measured between TB patients during DOTS treatment and non-TB control group.

SF-36 category	TB patients on DOTS ($n = 83$) Mean (SD)	Non-TB control ($n = 83$) Mean (SD)	Difference in mean	z value[a]	p value[a]
Physical functioning	53.5 (28.3)	86.4 (17.1)	32.9	−7.772	<0.001
Role physical health	49.2 (39.1)	84.3 (28.6)	35.2	−6.439	<0.001
Role emotional problem	47.5 (42.9)	86.3 (28.1)	38.9	−6.345	<0.001
Energy/fatigue	39.5 (25.5)	67.4 (28.9)	27.9	−5.813	<0.001
Emotional wellbeing	44.4 (24.7)	71.1 (25.5)	26.7	−5.954	<0.001
Social functioning	49.2 (25.9)	77.9 (29.7)	28.7	−6.519	<0.001
Pain	59.1 (29.5)	74.9 (31.8)	15.8	−3.839	<0.001
General health	44.2 (24.1)	71.3 (25.9)	27.2	−6.040	<0.001
Total score (QOL)	48.3 (30.0)	77.5 (26.9)	29.1	−6.104	<0.001

[a] Mann–Whitney U test.

Table 2 – Comparison of SF-36 scores of TB patients measured during and after completion of DOTS treatment.

SF-36 category	TB patients on DOTS ($n = 83$) Mean (SD)	TB patients after completion of DOTS ($n = 83$) Mean (SD)	Difference in mean	z value[a]	p value[a]
Physical functioning	53.5 (28.3)	85.4 (21.8)	31.8	−6.199	<0.001
Role physical health	49.2 (39.1)	88.4 (24.6)	39.2	−5.660	<0.001
Role emotional problem	47.5 (42.9)	88.8 (23.9)	41.4	−5.816	<0.001
Energy/fatigue	39.5 (25.5)	72.1 (16.8)	32.7	−6.472	<0.001
Emotional wellbeing	44.4 (24.7)	75.9 (16.3)	31.4	−6.708	<0.001
Social functioning	49.2 (25.9)	78.9 (19.5)	29.8	−6.417	<0.001
Pain	59.1 (29.5)	85.1 (19.2)	25.9	−5.352	<0.001
General health	44.1 (24.1)	71.8 (19.9)	27.6	−6.210	<0.001
Total score (QOL)	48.3 (30.0)	80.8 (20.3)	32.5	−6.104	<0.001

[a] Wilcoxon signed ranks test.

Table 3 – Comparison of SF-36 scores measured between TB patients after completion of DOTS treatment and non-TB control group.

SF-36 category	TB patients after completion of DOTS ($n = 83$) Mean (SD)	Non-TB control ($n = 83$) Mean (SD)	Difference in mean	z value[a]	p value[a]
Physical functioning	85.4 (21.8)	86.4 (17.1)	1.0	−0.180	0.857
Role limitation due to physical health	88.4 (24.6)	84.3 (28.6)	−4.0	−0.620	0.535
Role limitation due to emotional problem	88.8 (23.9)	86.3 (28.1)	−2.5	−0.040	0.968
Energy/fatigue	72.1 (16.8)	67.4 (28.9)	−4.7	−0.162	0.871
Emotional wellbeing	75.9 (16.3)	71.1 (25.5)	−4.8	−0.248	0.804
Social functioning	78.9 (19.5)	77.9 (29.7)	−1.0	−1.260	0.208
Pain	85.1 (19.2)	74.9 (31.7)	−10.2	−1.216	0.224
General health	71.8 (19.9)	71.3 (25.9)	−0.5	−0.823	0.411
Total score (QOL)	80.8 (20.3)	77.5 (26.9)	−3.3	−0.569	0.610

[a] Mann–Whitney U test.

study conducted by Awan et al.[11] reported that the HR-QoL was lesser than our study.

In the present study, 53.5 ± 28.3 and 85.4 ± 21.8 were the mean scores for 'physical function' of TB patients during DOTS treatment and after their DOTS completion, respectfully. Similarly, in all domains, the HR-QoL scores improved significantly after completion of treatment as seen in Table 2. Our study results were consistent with other studies.[12–16] However, studies conducted by Marra et al.[17] and Othman et al.[18] reported that the HR-QoL was lesser than our study. This finding suggests that social stigma is likely to influence the HR-QoL.

On comparing the HR-QoL at the onset of DOTS treatment and controls in the present study, overall initial HR-QoL (48.3 ± 30) was found lower than the control groups (77.5 ± 29.1) with significant difference ($p < 0.001$). Similarly, a systematic review published in 2009[19] and other studies using various tools of measuring HR-QoL among TB patients demonstrated that TB patients during their DOTS treatment had a lower HR-QoL than the healthy population.[12,17,20–22]

In the present study, HR-QoL of TB patients after DOTS completion was compared with the controls. The result showed that the overall mean score of HR-QOL among TB patients upon their DOTS completion and the control group was similar with no significant difference ($p > 0.05$). Even though the patient affected with TB started with a lower HR-QoL, the HR-QoL improved over the anti-TB treatment period and the overall HR-QoL score at the end of six months reached levels similar to the general population. In contrast, the study conducted by Mamani et al.[23] and Othman et al.[18] reported that the HR-QoL after DOTS treatment was lower than the general population with significant difference.

5. Conclusions

Patients with TB have significantly lower HR-QoL than compared to non-TB controls. The deficits in HR-QoL tend to be in all domains. However, after 6 months of drug therapy, large improvements in all HR-QoL domains were found. DOTS treatment significantly improved HR-QoL almost to the levels of non-TB controls. After successful treatment of TB, HR-QoL scores of TB patients were comparable to that of the general population. Therefore in future, TB patients should be counselled about the importance of DOTS and also efforts should be made to counsel and motivate their family members to ensure family support throughout the treatment period.

Conflicts of interest

The authors have none to declare.

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Original Article

Tuberculosis knowledge and attitude in aspiring doctors and nurses – Is it time for our TB teaching methods to evolve?

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ABSTRACT

Background: India accounts for nearly 24% of all the new tuberculosis (TB) cases globally. A good core knowledge and a positive outlook towards TB patients among our aspiring doctors and nurses are necessities for India to meet the Sustainable Development Goals (SDG) proposed by the WHO as a part of its post-2015 global TB strategy and to successfully combat the newer challenges posed by this disease in the future.

Aims: To evaluate knowledge related to transmission, prevention and treatment of tuberculosis amongst medical and nursing students. The study also aims to evaluate the attitude of students towards tuberculosis patients.

Methods: A self-administered pre-tested questionnaire was completed by 200 final year undergraduate medical and nursing students at a teaching medical college hospital. We collected information pertaining to general aspects of TB, its prevention and treatment and also the attitude of these prospective doctors and nurses towards treating/nursing TB patients.

Results: Most respondents (98.5%) were aware of the person to person transmission of the disease. 20% thought it could spread by fomites, 6.5% by shaking hands and 17% believed kissing could spread the disease. 72% of those surveyed did not think that healthcare workers were at greater risk of contracting TB. Only 52% of students knew that non-DOTS treatment was associated with a greater probability of patient defaults, development of drug-resistance, chronic disease and deaths. 27% of the students chose a simple surgical mask believing that it could protect them against nosocomial TB. Only 50% of nursing students were aware that the sputum smear examination was the diagnostic test required to label the patient as an 'open' or infectious case. A reluctance to interact with TB patients for fear of personal safety was seen in 28% of both groups. 83% of nursing students and 53% of the medical students were willing to attend to TB patients in isolation wards. 98.5% of the participants believed that TB is a disease that can be prevented, treated and cured.

Conclusion: There exists considerable scope for improving knowledge in areas relating to disease transmission and the preventive aspects of TB among our healthcare students. Since

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the present curriculum was deemed as adequate by the students, newer learning methods may be needed to disseminate any additional knowledge. Healthcare students did not display any prejudice towards TB patients which augurs well for TB control activities in the future.

1. Introduction

Tuberculosis (TB) is a major public health concern and is responsible for the largest number of deaths in the world from a single infectious cause. In 2014, the World Health Organization estimated that there were 9.6 million new cases of tuberculosis globally with the number of incident cases in India alone to be about 2.0–2.3 million. The tuberculosis mortality estimated for the same year was approximately 1.5 million deaths.[1] If the worldwide control of tuberculosis fails to improve, then the annual incidence of the disease by the year 2020 is expected to increase by 41%.[2]

A number of previous studies have shown large gaps in knowledge, attitude and practice regarding tuberculosis among practitioners from both the private and public sectors in India.[3–5] Interestingly, a similar deficit in tuberculosis knowledge was also observed among the clinical teaching faculty of a medical college who are generally responsible for imparting tuberculosis education to the future healthcare providers – medical students, nursing students and the paramedical staff.[6]

In 1997, the World Health Organization conducted a workshop on ''TB Control and Medical Schools'' which listed out specific recommendations regarding knowledge, skills and attitudes essential for a doctor to manage TB and suggested setting up a ''task force'' in each medical school to initiate the required changes in medical curriculum and practice.[7] Previous studies by Texeira et al. and Mehta et al. have shown a low level of tuberculosis knowledge among aspiring doctors.[8,9] However, Emili et al. in their study spread across medical schools in Canada, India and Uganda found the knowledge base and competency of undergraduate students to be adequate.[10] A study by Akin et al. showed both the level of tuberculosis knowledge as well as attitude of nursing students towards tuberculosis patients to be poor.[11] There is, therefore, a need to highlight the importance of tuberculosis in the undergraduate training curriculum to ensure that the students of healthcare graduate with the appropriate knowledge, skills and attitudes essential for the effective management of tuberculosis patients.

There is sparse literature on the level of tuberculosis knowledge among the medical and nursing students in their final (clinical) years in India. Hence, the present study aims to evaluate the knowledge about tuberculosis among undergraduate medical and nursing students in areas related to disease transmission, infection control and treatment strategies. The study also aims to assess the outlook of these aspiring doctors and nurses towards TB patients.

2. Materials and methods

2.1. Study design and setting

This questionnaire-based cross-sectional study was conducted among final year undergraduate medical and nursing students at a medical college teaching hospital located in Mangalore, India over a period of 2 months. This teaching hospital is a training area for both the medical and nursing training programmes running at the institute. Approval was taken from the Institutional Ethics Committee prior to the study.

2.2. Sample size

With 95% confidence interval, 80% power and 10% non-response, the sample size came to be approximately 200 using the following formulae:

$$N = \frac{z^2 pq}{e^2}$$

where N = sample size, z = 1.96 at 95% confidence level, p = percentage of prevalence of knowledge, attitude and practices in a previously studied population (52.6%), $q = 100 - p = 47.4$ and e = relative error which is considered to be 20% of p.

2.3. Data collection

A 20 point questionnaire-based survey was self-administered to 100 students in the final year of Bachelor of Medicine & Bachelor of Surgery (MBBS) and 100 students in the final year of Bachelor of Science – Nursing (B. Sc) who were willing to participate in the study and were present on the day when the questionnaire was administered. Students present on the study day but unwilling to participate were excluded. Convenient sample technique was used for sample selection. Informed written consent was obtained from all the subjects prior to participating in the study. The anonymity and confidentiality of the respondents was guaranteed. Students who agreed to participate in the study were expected to complete their questionnaires under supervision without allowance for discussions.

The multiple-choice based questionnaire consisted of 6 questions pertaining to general aspects of TB, 6 questions relating to prevention and treatment of TB and 7 questions evaluating the attitude of the respondents towards the disease. The student had to tick on all the correct options for his/her answer to be considered as a 'correct response'. The

Table 1 – Number of students with correct responses to the questions regarding general aspects of TB.

No.	Question	% correct response	
		Medical students (n = 100)	Nursing students (n = 100)
1.	Is the disease spread from patient to person? [Answer: Yes]	100%	97%
2.	How is TB transmitted? [Answer: through cough, sneeze of a TB patient]	52%	49%
3.	TB is caused by- [Answer: Microbes]	100%	95%
4.	Common symptoms of Pulmonary TB include- [Answer: cough> 2 weeks, hemoptysis, fever, night sweats, anorexia, weight loss]	96%	72%
5.	Who are most vulnerable? [Answer: HIV/AIDS, family members, healthcare workers, children 6–12 years age]	26%	19%
6.	Where are TB suspects referred to? [Answer: nearest DOTS centre]	98%	100%

questionnaire used for data collection in this study was critiqued and validated by a panel of in-house experts from the departments of Community Medicine and Public Health, Statistics, Internal Medicine and Pulmonology.

2.4. *Statistical analysis*

Data obtained from the questionnaires were tabulated using Microsoft Excel 2007 and were analyzed using the method of descriptive statistics and the results expressed as percentage of the total.

3. Results

3.1. *Demographic data*

A total of 200 students participated in the study of which 100 were final year medical students and 100 were final year nursing students forming two groups of equal size. 29% were males and 71% were females. 49% of medical students and 41% of nursing students had previously attended TB training in form of lectures, CME or TB workshops.

3.2. *Knowledge regarding general aspects of TB*

There were 6 questions testing knowledge regarding general aspects of TB (Table 1).

Most participants (98.5%) were aware of the fact that the disease could spread from person to person.

However, 20% (n = 40) respondents believed that the disease was transmitted by sharing drinking containers, eating utensils or food, 6.5% (n = 13) thought it could be transmitted by shaking hands with a TB patient and 17% (n = 34) considered kissing as one of the modes of transmission.

All medical students (100%) and 95% of nursing students considered TB to be an infectious disease caused by a microbe. Five students of nursing considered it to be a familial disease.

84% of participants (96% of medical students and 72% of nursing students) were able to correctly identify the common symptoms of TB.

72% of those surveyed (77 nursing and 67 medical students) did not think that healthcare workers were more predisposed to TB infection.

Awareness of the need to refer all ''TB suspects'' for evaluation to the nearest DOTS centre was observed in 99% of the participants.

3.3. *Knowledge regarding practice for prevention and treatment of TB*

The study questionnaire included 6 questions pertaining to preventive and treatment aspects of TB. Table 2 outlines the response of the study participants.

82% of nursing students and 91% of medical students were aware that multiple anti-TB drugs given in combination are

Table 2 – Number of students with correct responses to questions regarding prevention and treatment of TB.

No.	Question	% correct response	
		Medical students (n = 100)	Nursing students (n = 100)
1.	What is the treatment strategy used in TB patients? [Answer: Multiple anti-TB drugs in combination regimens]	91%	82%
2.	What are the consequences of unobserved TB-treatment? [Answer; Default, drug resistance, chronic disease and death]	71%	33%
3.	What information about TB treatment do you provide to TB patients?	* Read Text for Discussion	
4.	What type of mask would you prefer if exposed? [Answer:Disposable PR mask]	35%	56%
5.	Diagnostic test to label the patient as an ''Open or Infectious case'' is- [Answer: Sputum smear examination]	95%	50%
6.	Preventive Strategies- [Answer: 'cough etiquette', BCG in children, handwashing, use of protective mask]	50%	22%

Table 3 – Comparison of response of Medical students and Nursing students to questions regarding attitude towards TB.

No	Question	Response	All students *n* (%)	Medical students (%)	Nursing students (%)
1.	Is TB a major health threat?	• Yes	182 (91%)	100%	82%
		• No	8 (9%)	0%	18%
2.	Is it required to educate people with TB?	• Yes	198 (99%)	99%	99%
		• No	2 (1%)	1%	1%
3.	Do you involve yourself in educating people with TB?	• Yes	135 (67.5%)	57%	78%
		• No	64 (32%)	42%	22%
4.	Would you voluntarily choose to visit the Isolation Facility on regular basis to treat/provide nursing care for TB patients?	• Yes	136 (68%)	53%	83%
		• No	59 (29.5%)	43%	16%
		• NR[a]	05 (2.5%)	4%	1%
5.	Do you avoid interaction with TB patients fearing exposure/getting infected?	• Yes	56 (28%)	28%	28%
		• No	141 (70.5%)	71%	70%
		• NR	03 (1.5%)	1%	2%
6.	''TB can be prevented, treated and cured''- do you agree?	• Yes	197 (98.5%)	100%	97%
		• No	02 (1%)	0%	2%
		• NR	01 (0.5%)	0%	1%
7.	Is the present curriculum giving adequate information about TB to the students in healthcare?	• Yes	178 (89%)	87%	91%
		• No	18 (9%)	10%	8%
		• NR	04 (2%)	3%	1%

[a] NR = not response.

the treatment of choice in TB. 10% of nurses and 1% of doctors thought that single anti-TB drug would suffice for treatment of this disease. 25% of nurses in training and 9% medical students considered broad spectrum antibiotics as an effective treatment strategy. A small minority (1%) replied that they were unaware of the treatment.

52% respondents (33 nursing and 71 medical students) were aware that non-observed, i.e. non-DOTS treatment had a high likelihood of leading to defaults, development of drug-resistance, chronic disease and death.

Medical students fared better than their nursing counterparts in patient education on all parameters, namely treatment options (66% versus 47%), duration of treatment (86% versus 36%), frequency of administration (80% versus 30%), common medication related adverse events (76% versus 21%), importance of sputum examination (65% versus 23%), TB drugs and sputum examinations are free of charge in DOTs (68% versus 56%), consequences of treatment default (77% versus 27%) and importance of treatment compliance (76% versus 36%).

More nursing students ($n = 56$) than medical students ($n = 35$) preferred a disposable PR mask for protection. 27% students chose a standard surgical mask for protection. 95% of the medical students were aware that the diagnostic test needed to label a patient as an ''open'' or infectious case is sputum smear analysis whereas this awareness was seen in only 50% of the nursing students. The following preventive strategies were opted by the students (in descending order): practicing proper ''cough etiquette'' (80.5%), BCG vaccination (69.5%), hand washing (47.5%), use of mask (72.5%), avoiding hand shaking (8%), avoiding sharing dishes (14%) and practicing safe sex (6.5%).

3.4. *TB: Attitude of students in healthcare*

The questionnaire had 7 questions to test the attitude of students in healthcare towards TB (Table 3).

A majority of nursing students (82%) and all the medical students (100%) agreed that TB was a major health threat.

Although only 78% of nursing students and 57% of medical students were involved in patient education, yet both groups (99%) felt that there was a need to educate people about TB.

Nearly an equal number in both groups (28%) avoided interacting with TB patients fearing exposure and infection. But nursing students were more willing to render their services for TB patients in isolation wards than medical students (83% versus 53%).

A large proportion of participants ($n = 197$, 98.5%) believed that TB is a disease that can be prevented, treated and cured. 89% respondents believed that present curriculum gave them adequate information about the disease.

4. Discussion

In the present study, a majority of respondents (98.5%) were aware that TB could spread from person to person. However, the fact that the disease is spread by aerosolisation of droplet nuclei by cough/sneeze was known to only 50.5% of the students. 20% of those surveyed believed that it could be transmitted by sharing food, cooking vessels or drinking utensils; 6.5% felt that it could spread by shaking hands with a TB patient and 17% believed that kissing could spread the disease. Similar misconceptions about TB transmission in healthcare professionals have been reported in earlier studies

as well. A previous study by Jackson et al. revealed that about 8.6% of healthcare workers were unaware about TB transmission by coughing. In their study, 6.4% thought it to spread by body fluids, 1.4% by fomite and 0.5% by food.[12] A recent study showed that sharing items of personal use, skin contact and kissing TB patients under treatment was believed to transmit the disease by 97.2%, 38.9% and 88.6% by undergraduate nursing students respectively.[13] A study by Teixeira et al. revealed that 10.3% of the medical students (24.3% in preclinical years and 2.4% in clinical years) were unaware about coughing as a mode of transmission of TB.[14] A previous survey conducted among nursing students had concluded that 55.6% had average knowledge about tuberculosis and 59.1% knew about the transmission of the disease.[15] Although our study population included final year students in Medical and Nursing schools (who have clinical postings in hospitals), only 52% of medical students and 49% of nursing students could give the correct response to the question relating to various methods of TB transmission. 84% of students were aware of the common symptoms of TB. Nearly 98% were aware that all ''TB suspects'' need to be referred to the nearest DOTS centre for a complete evaluation. In this context, our figures stand better as compared to a study done amongst undergraduate students in a health facility in Columbia which showed that only 43.5% and 48.2% identified the risk factors and recognized the diagnostic criteria for tuberculosis respectively and nearly 51% were unaware of the DOTS strategy.[16]

In general, knowledge about diagnosis and treatment of TB was fairly good in both groups. Although sputum smear microscopy by Ziehl-Neelsen staining is the diagnostic tool used to identify the sputum positive cases in the RNTCP diagnostic algorithm, only 50% of our nursing students were aware that sputum smear examination is the diagnostic test of choice to label the patient as an ''open/infectious'' case. 95% of the medical students could correctly identify sputum smear examination for acid fast bacillus as the single test to confirm infectious pulmonary TB cases. This is better when compared to a study undertaken among interns in Delhi wherein only 65.9% of the respondents correctly chose sputum smear examination as the single most confirmatory test for diagnosing pulmonary TB. The others either did not respond (1.4%) or gave incorrect responses (including ELISA – 17.0%, PCR – 9.8%, X-ray chest – 4.2%, ESR – 1.7%).[17] Our study could identify gaps in awareness of preventive aspects of tuberculosis amongst healthcare students. Only 22% and 50% of nursing and medical students respectively could correctly identify all the preventive strategies for TB. Nurses (56%) fared better than medics (35%) in choosing the correct mask for personal protection. Our nursing students fared better when compared to a similar population in Sao Paulo in which 100% respondents did not choose sputum smear microscopy as a first test to identify pulmonary TB and 36.1% wrongly chose a surgical mask for individual protection.[13] This assumption by healthcare students that simple surgical mask gives complete protection from TB may make them more vulnerable to nosocomial infection. A study in Brazil showed that nearly two-thirds of undergraduate medical students displayed risky behaviour by not wearing masks when examining pulmonary TB patients and this figure only improved marginally to one-half in late clinical years. Thus, paradoxically knowledge about TB transmission was inversely associated with the use of masks.[8] In yet another study involving final year medical students and interns in India, it was observed that the correct responses were highest in questions related to diagnosis (73.12%), epidemiology (62.16%) and management (61.75%) whereas the risk perception towards tuberculosis was poor with only 28.5% of students having answered correctly. Only 6% of the students were even aware that a N 95 mask would protect them from contracting TB infection.[18]

Most students displayed a positive attitude towards TB and TB care, which in future, could translate into improved treatment success rates and better TB control in our country. Whereas 91% agreed that TB is a major health threat, most (98.5%) also believed that the disease could be prevented, treated and cured which reflects positivity in attitude. Less than one-thirds in both groups chose to avoid TB patients for fear of personal safety. More students in nursing (83%) than medical students (53%) in our study were willing to offer their services to TB patients voluntarily. A previous study by Sumanee et al. showed that while most TB care providers had a positive attitude towards TB and TB care, most (58.49%) had a negative attitude towards TB patients.[19]

The present study has a few limitations. *First*, the results presented here were obtained from medical and nursing students enrolled in a single medical college. Hence, inferences from the study, though valid, should be generalized with caution since the small sample size may not reflect student behaviour across a large country like India. *Secondly*, the survey questions in the present study were derived from diverse sources because a standardized survey questionnaire for TB is currently not available in our country. Hence, it is possible that few of the questions would be difficult to understand and incorrect responses to these do not necessarily indicate a lack of knowledge or awareness.

5. Conclusions

To conclude, this study shows that students of both medicine and nursing in their final years had good basic awareness about TB and would not display any prejudice towards treating and caring for TB patients in the future. However, there still exists some lacunae in their knowledge pertaining to modes of transmission, identifying patient groups at high risk for TB, prevention strategies, their choice of mask for personal protection and their knowledge relating to consequences of interrupted and incomplete TB treatment. Since both groups felt that the present curriculum imparted adequate TB knowledge in the classroom setting, we feel that innovative active learning tools like problem-based learning and 'field training' at the DOTS centre could be used to improve the student performance in the above parameters. We propose that the healthcare students could be imparted a fully integrated training covering the clinical aspects, public-health teaching and the bio-medical elements of TB in a single module rather than being taught separately at different points of the students training (i.e. traditional 'sequential' teaching spread across para-clinical and clinical years).

Conflicts of interest

The authors have none to declare.

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Original Article

Novel risk factors and early detection of anti tubercular treatment induced liver injury—Looking beyond American Thoracic Society Guidelines

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ABSTRACT

Introduction: ATT remains the standard treatment for tuberculosis. Drug-induced liver injury (DILI) has been a long-standing concern in the treatment of tuberculosis (TB) infection.
Aims and objectives: To study the occurrence and risk factors of DILI in patients on ATT by regular clinical and biochemical monitoring.
Materials and methods: 200 patients, in whom ATT was started, were enrolled in the study. None of the patients with established risk factor for DILI as recognized by ATS guidelines was included in our study population. Regular clinical and liver function test monitoring was done at the commencement of ATT and then at 2, 4, and 8 weeks in the intensive phase subsequently at 4 and 6 months.
Results: DILI developed in 16 patients. Among those, 10 patients (62.5%) developed early DILI and 6 patients (37.5%) developed late DILI. Female gender and extrapulmonary tuberculosis were found to be associated with increased risk of ATT-induced DILI, whereas age, BMI, and serum albumin were not found to significantly increase DILI risk.
Conclusion: DILI is a common problem among patients on ATT in our population. Early detection not only reduces the risk of developing Hepatic Failure but also prevents mortality.

1. Introduction

Tuberculosis [TB] is a common, and in many cases lethal, infectious disease caused by various strains of mycobacterium, usually *Mycobacterium tuberculosis*. One-third of the world's population is thought to have been infected with *M. tuberculosis*.[1] In 2012, an estimated 8.6 million people developed TB and 1.3 million died from the disease (including 320,000 deaths among HIV-positive people). It is estimated that about 40% of the Indian population is infected with TB bacteria, the vast majority of whom have latent rather than active TB. India alone accounts for 26% of total cases in the world. Most cases continue to occur in the most productive age-group of 25–54 years.

Antituberculosis treatment (ATT) remains the standard treatment for tuberculosis. The most frequent adverse effects

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of ATT are hepatotoxicity, skin reactions, gastrointestinal, and neurological disorders. Drug-induced liver injury (DILI) has been a long-standing concern in the treatment of tuberculosis (TB) infection. The liver has a central role in drug metabolism and detoxification, and is consequently vulnerable to injury.[2] ATT-related hepatotoxicity ranges from hepatic adaptation to hepatocellular injury to acute hepatic failure.[2] Asymptomatic transaminase elevations are common during ATT, but hepatotoxicity can be fatal when not recognized early and when therapy is not interrupted in time.[3–5] Another aspect of DILI is that it decreases treatment effectiveness, because it significantly contributes to noncompliance, ultimately contributing to treatment failure, relapse or the emergence of drug-resistance.

Understanding of ATT-related DILI has been hampered by differences in study populations, definitions of hepatotoxicity, monitoring, and reporting practices.[6–9] Literature reveals that rate of DILI during standard multidrug treatment range from 2.3% to 28% world over.[10] Indian studies reveal that rate of ATT-induced DILI is 11.5%.[11,12] No significant difference in the hepatotoxic effects between thrice weekly regimen and daily basis regimen has been found.[13] Isoniazid, rifampicin, and pyrazinamide carry hepatotoxic potential. Pyrazinamide appears to be the most likely to induce hepatotoxic effects.[14] No hepatotoxicity has been described for Ethambutol or Streptomycin.[15]

The most accepted and detailed document on ATT-induced DILI is provided by American Thoracic Society (ATS). ATS recognized risk factors that predispose patients to develop ATT-induced DILI include:

1. Chronic ethanol consumption
2. Viral hepatitis
3. Pre-existing liver disease
4. Pregnancy/3 months post-partum
5. Concomitant hepatotoxic medications
6. Baseline abnormal ALT/AST/Bilirubin
7. Concomitant HIV
8. Age >35 years.

In such situations, alanine aminotransferase (ALT) monitoring is recommended and treatment should be interrupted and, generally, a modified or alternative regimen used for those with ALT elevation more than three times the upper limit of normal (ULN) in the presence of hepatitis symptoms and/or jaundice, or five times the ULN in the absence of symptoms. The usual approach as suggested by ATS includes:

1. After ALT returns to less than two times the ULN, Rifampin may be restarted with or without Ethambutol.
2. After 3–7 days, isoniazid may be reintroduced, subsequently rechecking ALT.
3. If symptoms recur or ALT increases, the last drug added should be stopped.
4. For those who have experienced prolonged or severe hepatotoxicity, but tolerate reintroduction with rifampicin and isoniazid, rechallenge with pyrazinamide may be hazardous. In this circumstance, pyrazinamide may be permanently discontinued, with treatment extended to 9 months, although pyrazinamide can be reintroduced in some milder cases of hepatotoxicity.

However, these risk factors do not explain fully why only few patients develop ATT-induced liver injury. Hence, lot of research has been done to identify other unrecognized risk factors which may warrant more frequent liver function tests and close monitoring to detect liver injury at the earliest in order to reduce incidence of ATT-induced liver injury and allow completion of treatment in patients of tuberculosis. Besides, some low risk patients may have asymptomatic liver injury that may go unrecognized while following ATS guidelines and prove fatal if ATT is continued in such patients. Thus, early and more frequent monitoring may be required to detect ATT-induced liver injury. Since tuberculosis is endemic in developing countries like India and ATT-induced liver injury complicates treatment and promotes drug resistance, more studies should come from Indian Subcontinent to formulate guidelines regarding monitoring of patients on ATT. In this regard, we conducted a study in Department of Internal and Pulmonary Medicine of our hospital, Sheri Kashmir Institute of Medical Sciences, J & K India, one of the busiest tertiary care institutes of North India.

2. Aims and objectives

1. To determine possible risk factors associated with ATT-induced liver injury apart from ATS recognized risk factors.
2. To determine the frequency of LFTs to detect ATT-induced liver injury at the earliest.
3. To determine the relevance of early detection of ATT-induced liver injury.

3. Materials and methods

All inpatients and outpatients who met inclusion criteria were put on daily regimen of anti tubercular treatment and drugs were given based on their body weight (isoniazid 5 mg/kg; rifampicin 10 mg/kg; pyrazinamide 25 mg/kg; and ethambutol 15 mg/kg). All these patients underwent routine assessment with serum ALT levels at baseline then at 2, 4 and 8 weeks in the intensive phase and 2 monthly thereafter up to 6 months of ATT. Patients who were diagnosed as cases of DILI, treatment was stopped with close clinical and biochemical monitoring and weekly ALT levels were done and hepatitis viral serology was done to rule out infective cause. Treatment was resumed once there was clinical and biochemical resolution of DILI according to ATS guidelines. Cases with infective cause were excluded from the study. Informed consent was obtained from each participant.

Exclusion criteria included:

1. Multi-drug-resistant [MDR] tuberculosis.
2. Extensively drug-resistant [XDR] tuberculosis cases.
3. Patients with known ATS recognized risk factors.
4. Patients who develop hepatitis during anti tuberculosis treatment and are found to have serological evidence of infectious hepatitis.
5. Patients not compliant with biochemical monitoring as devised for this study.

DILI may be symptomatic or asymptomatic and early or late. **Symptomatic DILI**: ALT elevation 3 times or more of upper normal limit in the presence of symptoms of hepatitis [anorexia, nausea, vomiting, abdominal pain or jaundice]. **Asymptomatic DILI**: ALT elevation 5 times or more of the upper normal limit in the absence of hepatitis symptoms. **Early DILI**: DILI within first 2 weeks of ATT. **Late DILI**: DILI after 2 weeks of ATT.

4. Results

Baseline characteristics of the studied population are given in Table 1. A total of 200 patients were recruited into the study based on inclusion criteria. Among these, 10 patients were lost to follow-up and thus a total of 190 patients were available at the end of the study. Out of these, 122 (64.2%) were male and 68 (35.8%) were female. Age distribution is shown in Fig. 1. 120 patients had pulmonary tuberculosis and 70 patients had extrapulmonary tuberculosis. Nine patients were underweight, 174 had normal BMI and 7 were overweight. Out of 190 patients, 83 had albumin level of <3.5 g/dl and 107 had albumin >3.5 g/dl. Out of 190 patients in the study group, DILI developed in 16 patients which constituted 8.4% of the study group. Among these, 10 patients (62.5%) developed early DILI (within 2 weeks of ATT institution) and 6 patients (37.5%) developed late DILI (after 2 weeks of ATT institution). Among the 10 patients developing early DILI, 5 patients were female and 5 male, whereas in the patients developing late DILI, 5 patients were female and 1 patient was male. In the early DILI group, 6 patients (60% of the early DILI group) had symptomatic DILI and 4 patients (40% of the early DILI group) had asymptomatic DILI. In the late DILI group, 4 patients (66.6%) had symptomatic DILI and 2 patients (33.3%) had asymptomatic DILI. One of the patients in early DILI group developed Acute Liver Failure and died despite supportive measures and stopping all ATT drugs. 15 patients in the DILI group tolerated reintroduction of ATT drugs (Fig. 2). In the early DILI group, 4 patients (40% of the early DILI group) had asymptomatic DILI while as in the late DILI group, 2 patients (33.3%) had asymptomatic DILI. One of these patients who developed asymptomatic DILI within first 2 weeks and tolerated reintroduction of ATT developed symptomatic DILI later in the course of therapy. Interestingly, this patient tolerated reintroduction of ATT 2nd time as well and went on to continue ATT. The mean age in the group who did not develop DILI was 45.99 ± 16.83 years and the mean age of DILI group was 47.31 ± 15.74 years. The age difference was statistically insignificant (p value 0.764). DILI developed in 16 patients which constituted 8.4% of the patient population. Ten patients

Table 1 – Baseline parameters of the studied population.

Baseline parameter		Total no. of patients
Age	<20 years	12
	21–60 years	146
	>60 years	32
Sex	Male	122
	Female	68
BMI	<18.5 kg/m^2	9
	18.5–24.9 kg/m^2	174
	≥25 kg/m^2	7
Serum albumin	<3.5 g/dl	83
	≥3.5 g/dl	107
Site of tuberculosis	Pulmonary	120
	Extrapulmonary	70
Total		190

Table 2 – Association of ATT induced liver injury with different risk factors analyzed in our study and statistical signification of ach association.

Risk factor		DILI			P value
		Present	Absent	Total	
Mean age	(In years)	47.31 ± 15.74	45.99 ± 16.83		0.764
Sex	Male	6	116	122	0.020
		4.9%	95.1%		
	Female	10	58	68	
		14.7%	85.3%		
BMI	<18.5 kg/m^2	0	9	9	0.736
		0%	100%		
	18.5–24.9 kg/m^2	16	158	174	
		9.2%	90.8%		
	≥25 kg/m^2	0	7	7	
		0%	100%		
Serum albumin	<3.5 g/dl	9	74	83	0.290
		10.8%	89.2%		
	≥3.5 g/dl	7	100	107	
		6.5%	93.5%		
		2.5%	97.5%		
Site	Extrapulmonary	13	57	70	<0.001
		18.6%	81.4%		
Total		16	174	190	
		8.4%	91.6%		

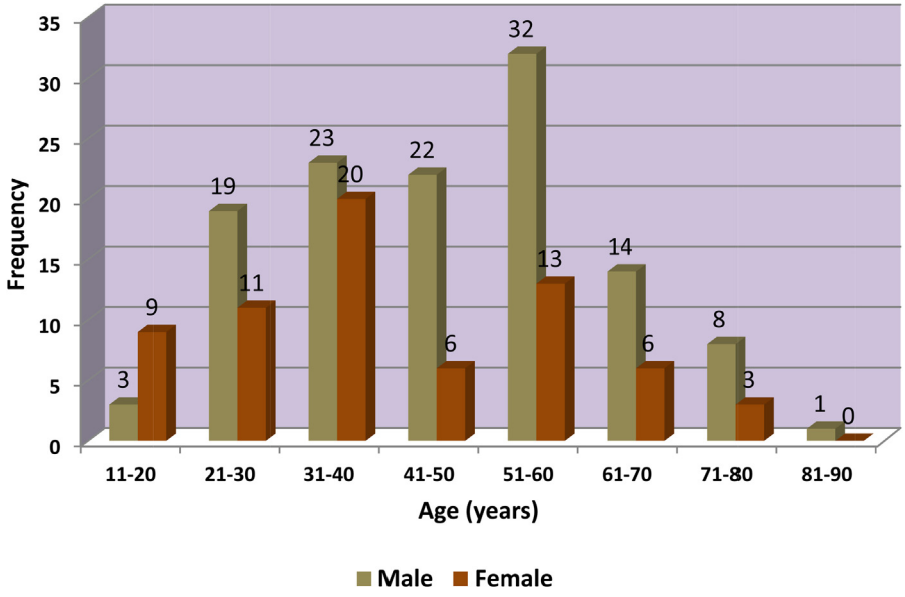

Fig. 1 – Age distribution of the study population.

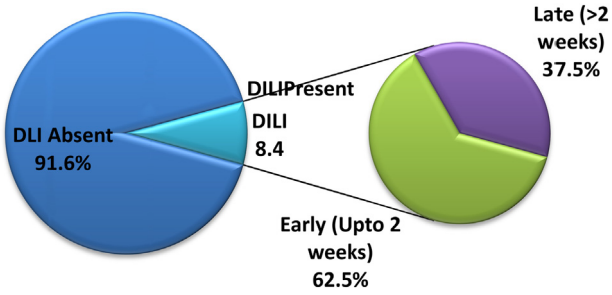

Fig. 2 – Early vs late ATT induced liver injury.

developing DILI were female and 6 patients developing DILI were male (Fig. 3). The gender difference was statistically significant (p value 0.020). Mean body mass index (BMI) in the group not developing DILI was 20.96 ± 2.10. Mean BMI in the DILI group was 20.79 ± 1.85. The difference in BMI was statistically insignificant (p value 0.736). 9 patients from the group with serum albumin <3.5 g/dl developed DILI, whereas 7 patients with serum albumin 3.5 g/dl developed DILI (Fig. 4). Serum albumin difference between the DILI and non-DILI group was statistically insignificant (p value 0.290). 3 patients (2.5%) with pulmonary tuberculosis developed DILI, whereas 13 (18.6%) patients with extrapulmonary tuberculosis devel-

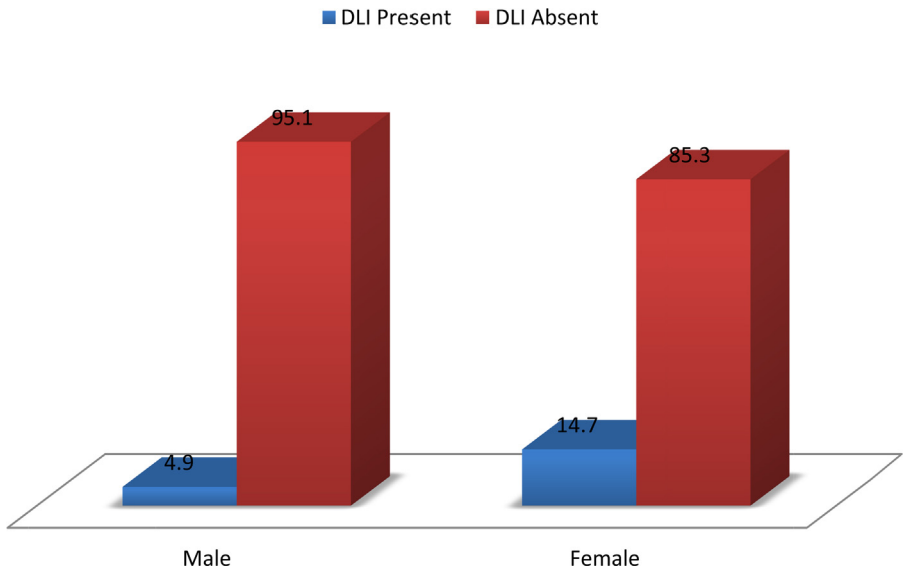

Fig. 3 – ATT induced liver injury and sex.

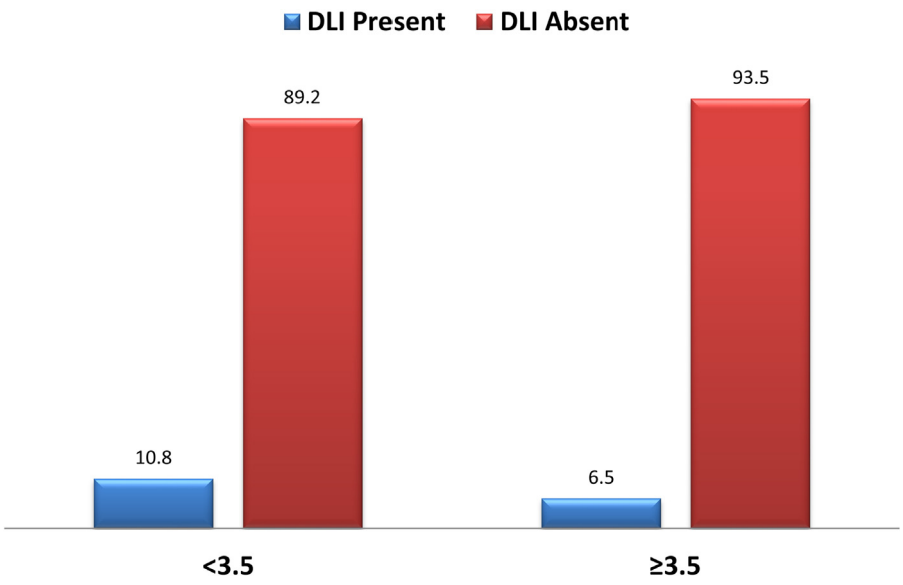

Fig. 4 – ATT induced liver injury and serum albumin.

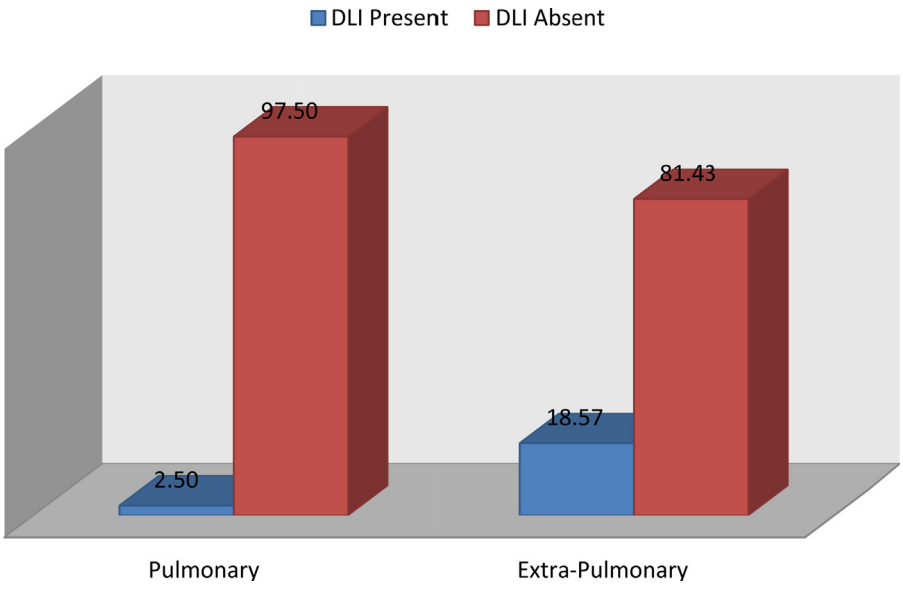

Fig. 5 – ATT induced liver injury and site of tuberculosis.

oped DILI (Fig. 5). Diagnosis as pulmonary and extra pulmonary tuberculosis was statistically significant (p value 0.001). The relation of different clinical variables with ATT induced liver injury is summarized in Table 2.

5. Discussion

DILI remains a major obstacle in the treatment of Tuberculosis as it decreases effectiveness because it significantly contributes to noncompliance, ultimately contributing to treatment failure, relapse, or the emergence of drug-resistance. The rate of occurrence of DILI due to ATT has been reported to vary from 2.3% to 28% in the literature. In our study, the prevalence of ATT-induced liver injury was 8.4%.[16–20] A higher risk of hepatotoxicity has been reported in Indian patients than in their Western counterparts. The reasons for this difference are unclear but could be due to slow acetylator status, malnutrition, higher prevalence of Hepatitis B and C, and other genetic and environmental factors in the Indian population. In addition, 15% of our patients developed transient elevation of liver enzymes during the course of treatment that settled on its own. The elevation in liver enzymes in these patients was never too high to qualify DILI diagnostic criteria and no

treatment interruption was required in these patients.[21] This has been widely reported in literature and is called Hepatic Adaptation.

Our study highlights the importance of monitoring of liver functions in all patients put on ATT. Six out of the sixteen patients who developed DILI in our study had no clinical symptom or sign suggestive of DILI. Such patients would have been missed had not we closely monitored liver function of all patients. Among these, one patient later on developed symptomatic DILI after reintroduction of ATT second time. However, the feasibility of routine liver function tests in a resource-limited country like India remains to be determined.

There is evidence that age has a role to play for development of DILI in ATT patients.[22–23] Some of the studies suggest that older age predisposes to ATT-induced hepatotoxicity. This is attributed to aging-related changes like decreased clearance of drugs metabolized by CYP450 enzymes, and changes in liver blood flow, liver size, drug binding, or distribution.[24,25] On the contrary, some studies suggest that younger age predisposes to ATT-induced hepatotoxicity. In our study, the mean age in the group who did not develop DILI was 45.99 ± 16.83 years and the mean age of DILI group was 47.31 ± 15.74 years. The age difference between the two groups was statistically insignificant (p value 0.764). So age did not play a significant role in predisposing patients on ATT to develop DILI in our study.[26–28]

Female gender is considered to be a predisposing factor for the development of drug toxicity due to ATT. This predisposition is particularly increased during pregnancy. Various explanations have been given for this increased risk of developing ATT-induced hepatotoxicity in female patients like increased cytochrome P450 3a activity in women, reduced glutathione synthesis during pregnancy, weight-based dosing of antituberculosis medications. In our study, 10 patients developing DILI were female. There was no pregnant patient in our study group. The gender difference in our study was statistically significant with p value of 0.020.[29]

Malnourished state reflected by low BMI and low serum albumin increases risk of developing ATT. It is due to altered metabolism of drugs due to poor nutritional state. This risk increases in patients with poor nutritional state receiving fixed adult dose combinations. In addition to this low, Mid Arm Circumference (MAC) is also an indicator of malnutrition and hence a predisposing factor development of ATT-induced DILI. In our study, although the mean BMI of the group developing DILI was low compared to the non-DILI group, the difference was statistically insignificant (p value 0.736).[30] Patients with pre-treatment hypoalbuminaemia have been found to be at higher risk of developing ATT induced liver injury. In our study, 9 patients from the group with serum albumin <3.5 gm/dl developed DILI whereas 7 patients with serum albumin >3.5 gm/dl developed DILI. The difference between the two groups was, however, statistically insignificant with p value 0.290.[31]

Extrapulmonary tuberculosis, especially abdominal tuberculosis, has been shown to be an independent predictor of ATT-induced liver injury, particularly in the Indians. In our study, 3 out of the 120 patients with Pulmonary Tuberculosis developed DILI whereas in patients with extrapulmonary tuberculosis 13 out of 70 patients developed DILI. This difference was statistically significant ($p < 0.001$). The reason for this difference remains unclear.

Our study thus signifies the importance of early and more frequent monitoring of liver functions in all patients of tuberculosis put on ATT. Such an approach helps in early detection of liver injury and timely intervention in these cases would certainly decrease the mortality and morbidity associated with ATT-induced liver injury. The authors thus recommend monitoring of liver functions biweekly in the intensive phase and every two months thereafter. This may apply to all patients put on ATT but in resource-limited countries; at least high-risk patients should be put on such protocol.

6. Conclusion

DILI is a common problem among patients on ATT in our population. This is a potentially life-threatening condition but preventable. Early detection and interruption of therapy is of utmost importance as is monitoring of liver functions. Most of these patients tolerate reintroduction of ATT successfully. Besides traditional risk factors, female sex and extrapulmonary tuberculosis are the two main risk factors for the development of DILI. Also, we suggest frequent clinical and biochemical monitoring (2 weekly in the intensive phase and 2 monthly thereafter) of the high-risk patients during the course of ATT.

Conflicts of interest

The authors have none to declare.

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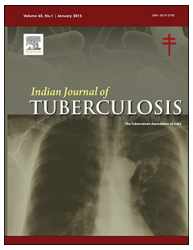

Original Article

Role of anti-tubercular treatment for positive endometrial aspirate DNA-PCR reproductive outcome in infertile patients in Indian setting – A randomized trial☆

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ABSTRACT

Aims: The aim of the study was to determine the effect of anti-tubercular therapy (ATT) versus no ATT on reproductive outcome in patients with positive endometrial aspirate DNA-PCR for tuberculosis.

Settings and design: Department of Obstetrics and Gynecology in collaboration with the Department of Microbiology at the All India Institute of Medical Sciences, New Delhi, India.

Methods and materials: This prospective randomized study was conducted on 100 women in the reproductive age group with primary or secondary infertility, attending the Gynecology OPD at AIIMS. Women with positive endometrial DNA-PCR, patent tubes on laparoscopy, and all other tests being negative for genital TB were randomized into two groups. In Group 1, patients received ATT for 6 months while in Group 2, patients were not given ATT. In patients who did not conceive a repeat endometrial sampling for DNA-PCR was performed at 6 months and 12 months post-laparoscopy.

Statistical analysis: It was carried out using Stata 11.0 (College Station, TX, USA).

Results: In Group 1 (ATT), 25 women achieved pregnancy with a pregnancy rate of 50% while in Group 2 (no ATT), 21 women achieved pregnancy with a pregnancy rate of 42% and the difference (95% CI) was 8.0% (−11.5%, 27.5%) which was not statistically significant ($p = 0.422$). Difference (95% CI) in the rate of repeat EA DNA-PCR being positive between the two groups at 6 months was 3.1% (−2.9%, 9.1%), $p = 0.299$, while at the end of 12 months, repeat DNA-PCR remained positive in 23 patients in Group 1 and in 26 patients in Group 2. Difference (95% CI) in the rate of repeat EA DNA-PCR being positive between the two groups at 12 months was 2.3% (−13.0%, 17.7%), $p = 0.767$.

Conclusion: The present study does not validate ATT for positive DNA-PCR; however, it does provide an evidence to stop over-treating patients on the basis of positive EA DNA-PCR even after they have received a 6 months course of ATT. Repeating PCR at 6 months and at

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12 months has no role and ATT should not be repeatedly given to the patient on the basis of repeat DNA-PCR alone.

Clinical trial registration number: CTRI/2015/10/006235, www.ctri.nic.in.

Key message

This study does not validate ATT for positive DNA-PCR; however, it provides evidence to stop over-treating patients even after receiving 6 months of ATT.

1. Introduction

The World Health Organization in 1993 declared tuberculosis, a common infectious disease in the Indian subcontinent, as ''a global emergency''.[1] Female genital tuberculosis (FGTB) is a chronic inflammatory process almost always secondary to a primary focus elsewhere in the body. When FGTB affects the genital organs in young infertile women, it can cause irreversible and permanent damage to the fallopian tubes, which is difficult to revert both medically and surgically. Genital tuberculosis is often asymptomatic and is reported to be a major pelvic factor causing infertility.[2,3] FGTB is incriminated in 5–15% of infertility among Indian women.[4,5] The incidence of genital tuberculosis in infertility has been reported to be higher in India up to 19%, and the incidence is still higher (41%) in tubal factor infertility.[6] Genital tuberculosis has a tremendous impact on the reproductive health in our country.

A definitive diagnosis of tuberculosis depends upon demonstration of the causative organism, *Mycobacterium tuberculosis* by acid-fast staining, and/or growth of the organism on Lowenstein-Jensen medium from a diagnostic specimen. Microscopic examination of acid-fast bacilli requires the presence of at least 10,000 organisms/ml of the sample, while culture is more sensitive requiring as little as 100 organisms/ml.[7,8] However, *M. tuberculosis* may take up to 8 weeks to grow in egg-based medium. Genital tuberculosis being a paucibacillary form of the disease, the smears and cultures are usually negative. Examination of stained smears has a very poor sensitivity of detection, reported as low as 0.4–1.23% among Indian women investigated for FGTB leading to infertility.[9,10] Similarly, isolation of acid-fast bacilli (AFB) has been reported to be possible in only 3.3–10.6% in endometrial samples.[11] The gold standard for identifying *M. tuberculosis* accurately is through culture. However, it has been observed that despite inoculation into multiple media, only 5.6% of samples yielded microbiological proof of the bacilli in suspected genital tuberculosis cases.[12] As far as imaging is concerned, hysterosalpingogram (HSG) is an initial procedure for evaluating tubal infertility and is a valuable tool in diagnosing female genital tuberculosis. FGTB was found in only 6.3% of patients who underwent hysterosalpingogram during investigations for infertility.[13]

Molecular diagnosis by DNA-polymerase chain reaction (PCR) is a useful adjunct in the diagnosis of female genital tuberculosis, which has abbreviated the time for definitive mycobacteriological detection to 1–2 days.[14] It has improved the sensitivity of detection of organisms, as PCR is a rapid, sensitive, and specific molecular biological method to detect mycobacterial DNA in both pulmonary and extrapulmonary samples from suspected tubercular patients. DNA-PCR of endometrial curettage specimens has been shown to have a high sensitivity (80%) and high specificity (70–92%) in the diagnosis of FGTB; thus, this test is useful in asymptomatic women with latent FGTB.[15] However, there are certain practical problems with DNA-PCR, the foremost being inability of DNA-PCR to differentiate between viable & nonviable bacilli.[16] DNA-PCR can be positive in latent/treated disease; hence, there is a risk of false positive results. False-positive rates by PCR are high as PCR can detect even single *M. tuberculosis* cells and may not be able to differentiate between infection and disease, as most of the Indian people may show positive PCR without suffering from the disease.

Sub-clinical genital tuberculosis can present as infertility alone and can be detected by the presence of DNA-PCR in the endometrium. Although DNA-PCR has revolutionized the diagnosis of paucibacillary-FGTB, yet there are a few unanswered practical questions – if a patient has no other symptoms/signs suggestive of FGTB and if all other tests are negative for FGTB, should the patient be treated with anti-tubercular therapy (ATT)? Some authors have suggested that PCR results should not be used to initiate or to stop ATT.[17] In a recent article, it has been advocated to start ATT on the basis of positive PCR only if there is some other evidence of FGTB on clinical examination, or presence of tubercles or other stigmata of TB on laparoscopy/hysteroscopy. In their opinion, PCR should be considered positive for TB only if associated with suggestive hysteroscopy or laparoscopy findings.[18] However, no randomized trials have been done to validate or disprove anti-tubercular treatment based solely on positive EA-DNA PCR if there is no other evidence of FGTB. Considering the lacunae in the available literature and hiatus in our understanding, we conducted this prospective randomized study to determine – whether giving anti-tubercular treatment solely on the basis of positive DNA PCR is justified in Indian scenario? The aim of the study was to determine the effect of anti-tubercular therapy (ATT) versus no ATT on reproductive outcome in patients with positive endometrial aspirate DNA-PCR for tuberculosis.

2. Subjects and methods

This randomized controlled clinical trial was conducted from November 2010 to May 2014 at the Department of Obstetrics

and Gynecology in collaboration with the Department of Microbiology at the All India Institute of Medical Sciences, New Delhi, India. An ethical clearance was obtained from the Institutes' Ethics Committee. All willing participants fulfilling the inclusion criteria were recruited in the study after obtaining their informed consent. Block randomization method was used to generate random numbers. There was no blinding in the study, that is, this was an open label study.

The inclusion criteria included women in the reproductive age group (20–40 years) with primary or secondary infertility and cohabiting with their husbands. Patients with positive endometrial DNA-PCR, with patent tubes on laparoscopy, and all other tests (EA-HPE, AFB, Laparoscopy) being negative for genital TB were included in the study. Patients above the age of 40 years with symptoms suggestive of genital TB except infertility and HSG suspicious of FGTB or genital TB diagnosed on basis of EA-histopathology, AFB smear, hysteroscopy, and laparoscopy findings were excluded from the study. Patients were randomized into two groups: Group I, where patients received ATT for 6 months and Group II, where patients were not given ATT. A total of 100 infertile women (50 in each group) as per inclusion/exclusion criteria were recruited.

A premenstrual endometrial aspirate (EA) was obtained using Karman's canula no. 4 attached to a 20 cc syringe (all disposables) for histopathology, acid-fast bacilli (AFB) smear, and DNA-PCR. Infertile women with a positive EA DNA-PCR but negative culture and smear underwent a diagnostic Laparoscopy and Hysteroscopy and findings were noted. We excluded women who had the presence of tubercles, caseation, beaded tubes, dense pelvic or peritoneal adhesions, hydrosalpinges, tubo-ovarian masses, and fibrosed or dilated tortuous tubes with cornual or fimbrial block.

ATT consisted of four drugs (Isoniazid, Rifampicin, Ethambutol, and Pyrazinamide) for the first two months in the intensive phase followed by two drugs (Isoniazid, Rifampicin) for the subsequent four months. It has now been proven that modern ATT has a low risk of teratogenicity, so these women were advised not to use any means of contraception while on ATT.

Subjects were encouraged for spontaneous conception in the initial 6 months post-laparoscopy and were advised timed intercourse. After six months post-laparoscopy, patients in both groups were given ovulation induction for 4 cycles with Clomiphene Citrate 100 mg for 5 days starting from day 2/5 of periods. They underwent follicle monitoring from day 8 onwards and received HCG injection 5000 IU I/M when the follicle size reached >18 mm and intrauterine insemination was done. In patients who did not conceive by then in both groups, a repeat endometrial sampling for repeat PCR test was performed at 6 months and 12 months post-laparoscopy. Follow-up period was 12 months post-laparoscopy.

Primary outcome: The patients in the two groups were compared for their reproductive outcome.

Secondary outcome: The patients in the two groups were compared for PCR negativity on endometrial aspirate after 6 months and 12 months post-treatment with ATT or no ATT after 6 months in the two groups.

3. Results

In total, 168 women were assessed for eligibility in our study and 100 were recruited into the study after providing informed consent. Reporting of this study follows the recommendations of the CONSORT statement (Fig. 1). Out of the 68 women who did not fulfill the inclusion criteria, 12 women had bilateral tubal blockage on laparoscopy and 15 women had unilateral blockage of either the left or the right tube. Three women had extensive adhesions on hysteroscopy, which required adhesiolysis. Twenty-two women had to be excluded as their husbands had male factor infertility. AFB smear was found positive in 2 and on histopathology, TB granuloma was present in 1. We had to exclude 8 patients as they were PCOS and 5 had endometriosis. One hundred women were randomized into two groups and allocated to intervention (Fig. 2).

As shown in Table 1, the baseline profiles were similar in Group 1 and Group 2. The menstrual irregularities in these women are shown in Table 2. Table 3 highlights the primary outcome of the study. In Group 1, 25 women achieved pregnancy with a pregnancy rate of 50% while in Group 2, 21 women achieved pregnancy (42%), and the difference was not statistically significant ($p = 0.422$). Also, we found that if a woman who is DNA-PCR-positive takes ATT, then she has a 1.19 times higher chance of becoming pregnant than a woman who is DNA-PCR-positive but does not take a course of ATT. In Group 2, there was one patient lost to follow-up after 22 weeks of gestation. She had conceived in the second cycle of ovulation induction and in her Level II ultrasound scan for anomalies, the fetus was found to have multiple congenital malformations.

Table 4 highlights our secondary outcome, namely the DNA-PCR status at the end of 6 months and 12 months in both the Groups. One patient in Group 1 and 2 in Group 2 refused the investigation for getting a repeat EA DNA-PCR at the end of 12 months. In our study, the rate of repeat EA DNA-PCR at 6 months showed a difference (95% CI) of 3.1% (−2.9%, 9.1%) between the two groups ($p = 0.299$) as shown in Table 4. Repeating endometrial aspiration for DNA-PCR at 12 months showed a difference (95% CI) of 2.3% (−13.0%, 17.7%) ($p = 0.767$).

The reproductive outcome (Table 3) and follow-up of repeat DNA-PCR at 6 and 12 months were not statistically significant in the two groups (Table 4). Also, no adverse event due to ATT (nausea, vomiting, deranged liver enzymes, etc.) was noted in either group.

Statistical analysis: It was carried out using Stata 11.0 (College Station, TX, USA). Data was presented as number (%) or mean ± SD (minimum–maximum) as appropriate. The continuous and categorical baseline characteristics were compared between the two groups using Student's 't' test and chi-square test respectively. The difference in the rate of pregnancy (primary outcome) and repeat EA DNA-PCR (secondary outcome) was compared between the two groups using proportion test. The results were presented as difference in proportion (95% CI). The p value <0.05 was considered statistically significant.

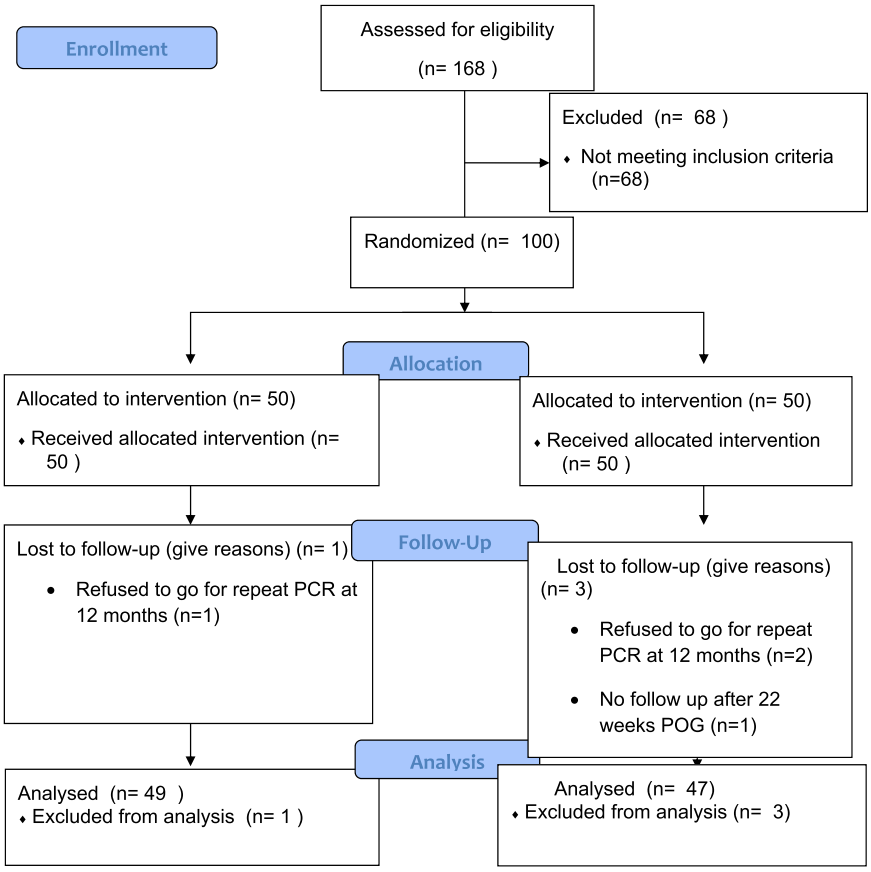

Fig. 1 – CONSORT flow diagram.

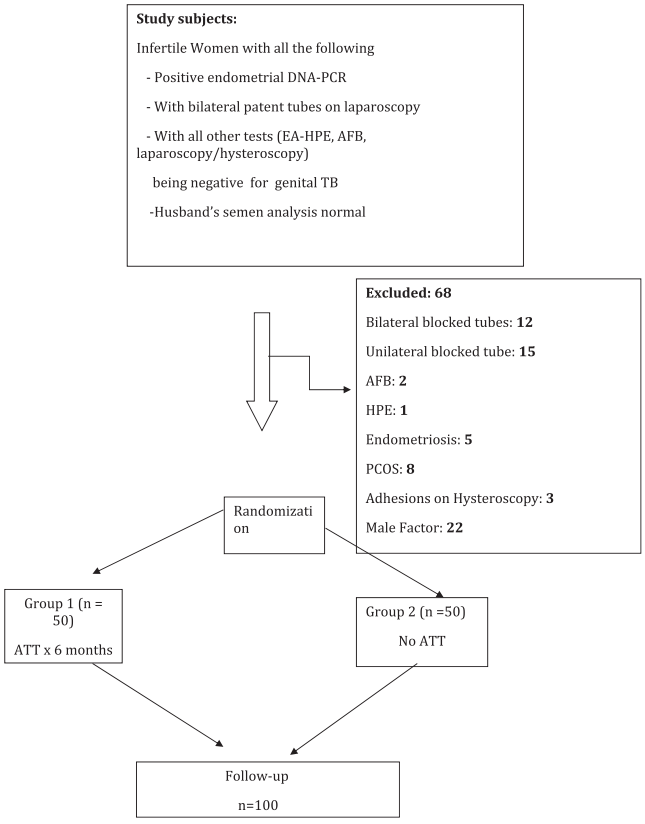

Fig. 2 – Methodology (flow chart).

4. Discussion

M. tuberculosis may remain latent in the basal endometrium before developing into active tuberculosis and continues to be missed even with available gold standard tests. Active genital Koch's may be diagnosed by hysterosalpingogram and laparoscopy, and the diagnosis of latent FGTB requires tests at the molecular level. PCR is a technique that is used to amplify extremely small amounts of a specific DNA genomic sequence. Being a biological method, it can increase the yield in clinical samples and detect genital TB earlier in the process. By amplifying the DNA of *M. tuberculosis*, PCR-based methods have proven to be very useful for rapid diagnosis, and it has been found to be the most sensitive technique in detecting even a picogram of DNA.[19] For a proper sampling for PCR, an invasive testing like an endometrial biopsy or even laparoscopy may be required. Considering the limited utility of histological and micro bacterial diagnostic methods, previous study conducted by Bhanu et al. demonstrated the benefit of PCR in the rapid and accurate diagnosis of FGTB.[16] Their study demonstrated DNA-PCR to be positive in 56% patients in contrast to 1.6% for AFB and 3.2% for routine culture. However, the results of PCR were not validated against the conventional methods.

In the present study, while handling the sample for DNA extraction and PCR, several concurrent negative controls were used with utmost care in separate rooms, in order to rule out

Table 1 – Demographic profile.

	Group 1 (ATT) $n = 50$	Group 2 (no ATT) $n = 50$	p value
Age in years (±SD, range)	28.92 ± 3.88 (21–39)	28.02 ± 3.74 (20–35)	0.240
Duration of infertility in years (±SD, range)	5.6 ± 4.3 (1–19)	4.5 ± 3.6 (1–18)	0.157
BMI in kg/m^2 (±SD, range)	23.2 ± 2.9 (18–32)	25.4 4.1 (15–33)	0.001
Primary infertility	32 (64%)	30 (60%)	0.680
Secondary infertility	18 (36%)	20 (40%)	

Table 2 – Menstrual irregularities.

	Group 1 (ATT) $n = 50$	Group 2 (no ATT) $n = 50$	p value
Regular	42 (84%)	39 (78%)	0.742
Hypomenorrhoea	6 (12%)	8 (16%)	
Oligomenorrhoea	2 (4%)	3 (6%)	
Withdrawal only	0	0	

Table 3 – Primary outcome: reproductive outcome.

	Group 1 (ATT) $n = 50$	Group 2 (no ATT) $n = 50$
Pregnancies	25 (50%)	21 (42%)
Difference in pregnancy rate = 8% (−11%, 0.27%) p = 0.4222		
Pregnancy outcome	$n = 25$	$n = 21$
1. Full term deliveries	21 (84%)	19 (90.5%)
2. Abortions	3	1
3. Ectopic	1	0
4. Anomalous fetus	0	1 (lost to follow up after 22 weeks of pregnancy)

Table 4 – Secondary outcome – repeat PCR at the end of 6 months and 12 months.

Repeat PCR at the end of 6 months

	Group 1 (ATT) $n = 50$	Group 2 (no ATT) $n = 50$
At 6 months pregnant	18	16
PCR done after 6 months	32	34
Positive PCR	31	34
Negative PCR	01	00

Difference (95% CI) in the rate of repeat EA DNA-PCR being positive between the two groups at 6 months was 3.1% (−2.9%, 9.1%) p = 0.299

Repeat PCR at the end of 12 months

	Group 1 (ATT) $n = 32$	Group 2 (no ATT) $n = 34$
At 12 months pregnant	07	05
PCR done after 12 months	25	29
Positive PCR	23	26
Negative PCR	01 + 01 (patient refused repeat PCR)	01 + 02 (patient refused repeat PCR)

Difference (95% CI) in the rate of repeat EA DNA-PCR being positive between the two groups at 12 months was 2.3% (−13.0%, 17.7%) p = 0.767

and minimize the possibility of contamination/false-positive results. As clinicians, we must remember that in a quality-assured laboratory set-up, the DNA-PCR test is highly reliable. However, there is paucity of concrete evidence in literature regarding initiation of treatment based on PCR alone. In a previous study on infertile women with repeated IVF failures, PCR was positive in 77.7% of participants and up to 20% of them conceived with IVF after the initiation of ATT on the basis of the positive PCR result.[20] Their finding indicates that the detection of latent GTB requires the use of molecular tests such as PCR. The authors advocated use of PCR only in women with repeated IVF failure and not on a routine basis because of cost restraints. In the study by Kulshrestha et al., the fertility outcome for women with GTB was good only when ATT was started early, thus making it imperative to diagnose tuberculosis early in infertile women.[21]

In our study, the pregnancy rate was 50% (25/50) in Group 1 and 42% (21/50) in Group 2. The reason for the pregnancy rate being high in our study is perhaps because the patients had very early subclinical disease/latent tubercular infection, without significant damage to the tubes and endometrium, which could hamper the chances of implantation and thereby

conception in a woman. In women with FGTB, once the cavity is destroyed by tubercular endometritis and synechiae formation, it is advisable to offer these couples adoption.

The present study has proved that repeating PCR at 6 and 12 months has no role and clinicians must avoid injudicious use of ATT. It is harmful to patients and to the community at large by building resistance to the drugs. ATT should not be repeatedly given to patients on the basis of repeat DNA-PCR alone as patients receiving ATT may remain PCR positive for a time despite mycobacterial sterilization.[16,22–24] Based on their results, Thangappa et al. concluded that a positive PCR should be given due importance and infertile women should be considered as having genital Koch's and treated accordingly.[25]

In recent literature, there is evidence to suggest that infertile women without tubal or endometrial damage can be given anti-tubercular treatment based on a positive endometrial TB-PCR as it has been shown to have a favorable chance of early conception.[26] Jindal et al. instituted anti-tubercular therapy to infertile women with no demonstrable cause other than a positive endometrial TB-PCR test, which highlighted the presence of sub-clinical disease. The authors concluded that infertile women with a positive endometrial TB-PCR without any clinical evidence of disease reliably detects sub-clinical genital tuberculosis that leads to infertility and starting appropriate ATT before the damage occurring to any of the pelvic organs can reverse the early but subtle damage caused by the bacilli *M. tuberculosis*.[26]

As clinicians, in a country like India with a high prevalence of genital tuberculosis, instituting appropriate ATT for asymptomatic or doubtful sub-clinical TB can be justified on the basis of significant risk of progression of the disease, damage to or loss of function of a vital reproductive organ, that is, uterus and tubes.

Drug resistance is a primary concern when prescribing ATT to women who have no other evidence of the disease except EA DNA-PCR-positive. Resistance to Isoniazid (INH) and Rifampicin (RIF) is worrisome, as it requires the use of second-line drugs, which are difficult to procure, far more toxic, and expensive compared to first-line therapy. Another reason for developing drug resistance can be due to its prolonged treatment of over six months and non-compliance of the patient as well as social stigma. Side effects like drug-induced hepatitis and peripheral neuritis can be reasons for discontinuation of therapy.

Thus, an early diagnosis helps in preventing/minimizing the damage to the genital organs. In future, large randomized trials must be planned to evaluate the semen of the male partners of these infertile women to study if there is transmission of genital Koch's. Immuno-histochemical (IHC) evaluation of the endometrium for pathological changes must be planned with the aim to pick up early lesions of genital tuberculosis.

5. Conclusion

The present study does not validate ATT for positive DNA-PCR; however, it does provide an evidence to stop over-treating patients on the basis of positive EA DNA-PCR even after they have received a 6 months course of ATT, which has been the practice at some centers due to lack of clinical trials. This study is of national interest that will go a long way in improving the reproductive health of infertile women with FGTB and may also improve their chances to conceive when the disease is picked up early, in its latent stage when irreparable damage to the reproductive organ has not been done.

Compliance with ethical standards: ethical approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

We have attached the letter from the Institute's Ethics Committee.

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Conflicts of interest

The authors have none to declare.

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Short Communication

Smoking and alcohol consumption: Risk factors for pulmonary tuberculosis among the tribal community in central India

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ABSTRACT

Smoking and alcohol consumption are important risk factors for pulmonary tuberculosis (PTB). A cross-sectional survey was undertaken among the Gond tribe in Jabalpur district of Madhya Pradesh, and information on smoking and alcohol consumption was collected. As compared to females, males had an increased odds for PTB prevalence (odds ratio (OR) 3.2; 95% CI 486.4–1358.4; $p = 0.01$). Similarly smokers and alcohol consumers had an increased odds for PTB compared to non-smokers and non-alcohol consumers, respectively [(OR 3.2; 95% CI 516.4–1986.4; $p = 0.003$); (OR 3.2; 95% CI 480.8–2254.8; $p = 0.009$)]. Persons who were both smokers and alcohol consumers had an equally increased odds of PTB than those who did not smoke and consumed alcohol (OR 4.1; 95% CI 477.6–2581.6; $p = 0.001$). The study findings highlight the need to develop and implement culturally appropriate awareness raising activities among the tribal community to support TB control efforts.

1. Introduction

India remains the highest tuberculosis (TB) burden country in the world and accounts for one fifth of world's new TB cases and two thirds of the cases in the South-East Asia region.[1] Though many biological, socio-economic, and behavioral risk factors are known to be associated with the development of pulmonary TB (PTB), tobacco smoking and alcohol use are important risk factors for TB.[2]

In the central Indian state of Madhya Pradesh (MP), the tribal population accounts for about a quarter of the total population of the state. The various tribes living in MP have been categorized into 46 ethnic groups, with the Gond tribe being one of such groups. Of the four taluqs (an administrative subunit) in the Jabalpur district of MP, Kundam is a tribal – mostly Gond – dominated taluq, with ≈70% of the overall population belonging to the Gond tribe. A recently conducted TB disease prevalence survey in Jabalpur district observed a higher prevalence of TB disease among the tribal compared to the non-tribal populations.[3] In view of this, studying the risk factors in specific tribal populations assumes relevance, especially as there is no information on the risk factors for PTB disease among the tribal population of the area, such as the Gond. This paper presents results on whether tobacco smoking and alcohol consumption is associated with the

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development of PTB disease among the Gond tribal population in Jabalpur district, Madhya Pradesh state.

2. Methods

As part of the TB disease survey in Jabalpur district, this cross sectional study was conducted in Kundam taluq during 2009–2010. The proportionate sample size for the taluq was estimated as 4479 individuals aged ≥15 years. A random sample of villages was selected to cover the required sample for TB disease survey. The details of the disease survey have been described in its published report.

During the TB disease survey, additional information on tobacco smoking and alcohol consumption was collected from the study population and recorded on a pre-tested and a pre-coded cards by trained investigators. All the completed cards were scrutinized, checked, and computerized by trained data entry operators. Prevalence of disease was compared between exposed and non-exposed groups. The odds ratio (OR) was used as the effect measure. The OR was calculated by measuring the ratio of the prevalence odds of the exposed and non-exposed groups for each risk factor using SPSS 13.0 software (SPSS Inc., Chicago, IL, USA). Informed written consent was obtained from all individuals included in the survey. The ethics committee of the institute approved the study.

3. Results

Of the total 4079 individuals eligible for screening, 3903 (95.7%) were screened for chest symptoms. The prevalence of smoking and alcohol consumption was found to be 22.5% and 16.9% respectively. Males had a significantly higher prevalence of both smoking and alcohol consumption (874; 47.4% and 627; 34.0%) than females (5; 0.2% and 31; 1.5%) ($p < 0.01$).

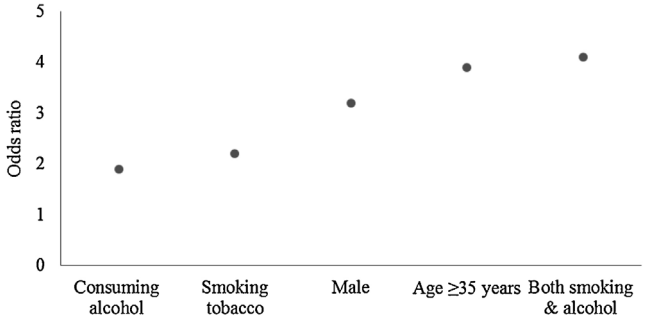

Fig. 1 – Association between pulmonary tuberculosis and odds of risk factors.

The overall prevalence of PTB was 589.3 per 100,000 (95% CI: 349.3–829.3). Table 1 describes the factors associated with PTB. Persons aged >35 years had 3.9 times higher odds of developing TB than persons aged ≤35 years. When compared to female, male had an increased odds for PTB prevalence (OR 3.2; 95% CI 486.4–1358.4; $p = 0.01$). Smokers and alcohol consumers had an increased odds for PTB when compared to non-smokers and non-alcohol consumers respectively [(OR 3.2; 95% CI 516.4–1986.4; $p = 0.003$); (OR 3.2; 95% CI 480.8–2254.8; $p = 0.009$)]. Persons who were both smokers and alcohol consumers had an increased odds of PTB (Fig. 1) than those who did not smoke and consumed alcohol (OR 4.1; 95% CI 477.6–2581.6; $p = 0.001$).

4. Discussion

The study found a significantly higher prevalence of tobacco smoking and alcohol consumption among this ethnic group as compared to the prevalence in the general population of Madhya Pradesh (smoking: 22.5% vs 11.9%, $p < 0.001$; alcohol:

Table 1 – Selected risk factors associated with PTB disease.

Risk factors	Eligible to screen	Total screened	TB cases	Prevalence/ 100,000 95% CI	Crude POR	*p*-value
Age in years						
≤35	2089	2016	5	248.0 (31.0–465.0)	1	
≥35	1990	1887	18	953.9 (514.9–1392.9)	3.9	0.003
Sex						
Female	2118	2060	6	291.3 (58.3–524.3)	1	
Male	1961	1843	17	922.4 (486.4–1358.4)	3.2	0.01
Tobacco smoking						
Non-smoker	3184	3024	12	396.8 (172.8–620.8)	1	
Smoker	895	879	11	1251.4 (516.4–1986.4)	3.2	0.003
Alcohol consumption						
Non-consumers	3408	3245	14	431.4 (205.4–657.4)	1	
Consumers	671	658	9	1367.8 (480.8–2254.8)	3.2	0.009
Tobacco smoking and alcohol consumption						
Nil	3047	2889	11	380.7 (155.7–605.7)	1	
Tobacco smoking only	361	356	3	842.7 (107.3–1792.7)	2.2	0.21
Alcohol consumption only	137	135	1	740.7 (705.3–2186.7)	1.9	0.51
Tobacco smoking and alcohol consumption	534	523	8	1529.6 (477.6–2581.6)	4.1	0.001

16.9% vs 10.3%, $p < 0.001$). Further, our analysis shows that men had a higher risk of PTB than women that has been reported in earlier studies.[4,5] This could be due to the higher prevalence of smoking and alcohol use among males observed in the present study.

Tobacco smoking and alcohol use are highly prevalent in India particularly among men.[6] Ours is the first kind of study which specifically assessed the association of tobacco smoking and alcohol consumption with PTB among the *Gond* tribal community in central India. This finding is concordant with other studies done among non-tribal population in India and other parts of the world.[7–9] As a risk factor of PTB, tobacco smoking has increased substantially over past three decades, especially in developing countries. The population attributable risk for several risk factors in 22 high TB burden countries has estimated that active smoking is responsible for 23% of the TB incidence.[10] Our study findings also show that tobacco smoking and/or alcohol consumption are significantly associated with the development of PTB in this ethnic group. However the association between smoking and TB, which has been shown to exist in different studies, has not yet received sufficient attention in terms of TB care particularly in India.

An understanding of the epidemiological relationship between smoking and TB is important because both smoking and TB cause extensive morbidity and mortality worldwide. Potential mechanisms for smoking and TB, likely to involve are both structural changes affecting lung function and altered immune response.[11] The other likely possibility is that nicotine turns off the production of TNF-alpha by the macrophages in the lungs, rendering the patient more susceptible to the development of progressive disease from latent Mycobacterium tuberculosis infection.[12]

Alcohol consumption is (another one of the behavioral risk factors) found to be associated with the PTB. Alcohol has been accepted as a risk factor by similar studies done in developed countries such as Australia, Canada and USA.[13–15] The reason for the risk of active TB in people, who drink alcohol, was explained that due to both increased risk of infection related to specific social mixing patterns among alcohol consumers, as well as influence on the immune system of alcohol itself.

Although, the independent relation of tobacco and alcohol with PTB has been known, the relative contribution of tobacco and alcohol use to the risk of PTB is less studied and discussed. The explored co-relation between these all factors to PTB could be an important key for making new policy to control TB. The present study shows that persons who both smoked and consumed alcohol had 4.1 times higher odds of developing PTB than those who did not smoke and consumed alcohol. The association of smoking as well as alcohol consumption with TB has been reported by other workers.[16,17] With the observed association between tobacco smoking, alcohol consumption and PTB disease in this tribal population, there is an urgent need to implement the WHO Framework Convention on Tobacco Control (WHO FCTC), including culturally appropriate awareness raising activities to target tobacco smoking and alcohol consumption, and ensuring tobacco cessation services are available to support the efforts to control TB in this tribal community.[18]

5. Limitations of the study

We did not investigate the potential role of other risk factors. While assessing the effects of the selected risk factors, the confounding effects of these other factors, therefore, could not be controlled for. Also, the findings are based on the cross-sectional survey leading to the possibility of recall bias. These might have resulted in an overestimation or underestimation of the true results.

6. Conclusion

The findings of the study indicate that tobacco smoking and alcohol consumption are significantly associated with PTB disease in this ethnic population. There is an urgent need to develop and implement culturally appropriate awareness raising activities to target tobacco smoking and alcohol consumption to support the efforts to control TB in this community.

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Authors' contribution

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

Conflicts of interest

The authors have none to declare.

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Case Report

Black brown discoloration and hairy tongue – A rare linezolid side effect

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ABSTRACT

Introduction: Linezolid was approved for clinical use for methicillin resistant *Staphylococcus aureus* and vancomycin-resistant *Enterococci*. Additionally it is used in the management of drug resistant tuberculosis. It is well-tolerated however bone marrow suppression and neuropathies may occur in patients taking this antibiotic for more than 2 weeks. Black discoloration and black hairy tongue (BHT) due to linezolid is rarely reported. We report two cases of BHT.

Case reports: Two patients of drug resistant pulmonary tuberculosis developed benign hairy tongue with linezolid 600 mg per day. In both the cases black colored/hairy tongue was reported within 2–3 weeks of linezolid treatment. Both patients improved after withdrawal of linezolid. Subsequent reintroduction of linezolid with good oral hygiene was well tolerated and both patients completed the treatment of 2 years duration without any recurrence.

Conclusion: Black discoloration and BHT is a rare but transient adverse reaction with linezolid. Reintroduction of linezolid with good oral hygiene is well tolerated.

1. Introduction

Linezolid, member of the oxazolidinone antibiotic class, inhibits protein synthesis by binding the 23S ribosomal RNA (rRNA) portion of the bacterial 50S ribosomal subunit. In adults, linezolid is administered at a dose of 600 mg twice daily. Data on longer-term use are limited, but serious neuropathies e.g. peripheral and optic neuropathies, myelosuppression, and hyperlactatemia have been observed[1–3] and are considered to be related to the inhibition of mitochondrial protein synthesis.[3] Linezolid is classified as group 5 drug for the management of drug resistant tuberculosis (DRTB) by WHO. Linezolid exhibits in vitro bacteriostatic activity against *Mycobacterium tuberculosis*, including multidrug-resistant (MDR) and extensively drug-resistant (XDR) strains, with a minimum inhibitory concentration of less than 1 μg per milliliter.[4–7] It is well-tolerated with nausea, vomiting, diarrhea and headache being the most commonly reported side effects. Bone marrow suppression and neuropathies may occur in patients taking this antibiotic for more than 2 weeks. Linezolid-induced BHT has rarely been reported. Black hairy tongue (BHT) is a benign disorder characterized by hypertrophy and discoloration of the filiform papillae of the tongue. This disorder has been associated with numerous medications and predisposing conditions. We report two cases of BHT believed to be caused by linezolid.

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2. Case 1

A 25-year-old male patient of XDR pulmonary TB weighing 80 kg attended the Out Patient Department. He was prescribed injection capreomycin, cycloserine, moxifloxacin, linezolid, ethionamide and para-amino salicylic acid (PAS). Linezolid was given 600 mg once daily. He was tolerating medicines well. On follow-up visit at 1 month he complained of black discoloration of tongue after 10–15 days of starting the treatment (Fig. 1a). Linezolid was suspected to be the culprit drug for this black discoloration as no other anti-tubercular drug was known to cause it and there were few case reports of BHT due to linezolid. Linezolid was withheld and the tongue became normal in 15 days (Fig. 1b). Linezolid 600 mg OD was reintroduced after 7 days of clearing of tongue with no recurrence and the drug was continued for next 2 years without any event.

3. Case 2

A 30-year-old female patient weighing 45 kg with proven MDR pulmonary TB was started on Inj kanamycin, cycloserine, ethionamide, moxifloxacin, PAS and linezolid. Linezolid was given 600 mg once daily. She developed brown black discoloration of tongue 15 days after starting treatment, which went on increasing and she consulted after a month of treatment (Fig. 2a). Linezolid was suspected to be culprit drug and was withheld. She was advised for oral hygiene and tongue cleaning by tongue cleaner or soft brush. The tongue cleared of discoloration after 10 days (Fig. 2b). The drug was reintroduced after 7 days of clearing of tongue with no recurrence of discoloration of tongue and patient completed 2 years therapy without any adverse events.

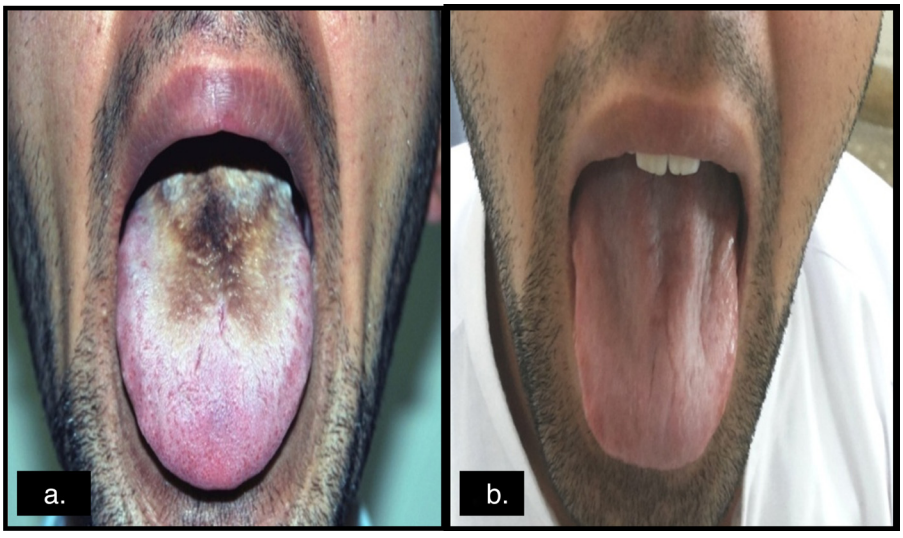

Fig. 1 – (a) Black hairy tongue in case 1 taking linezolid. (b) Normal and clean tongue after withdrawal of linezolid.

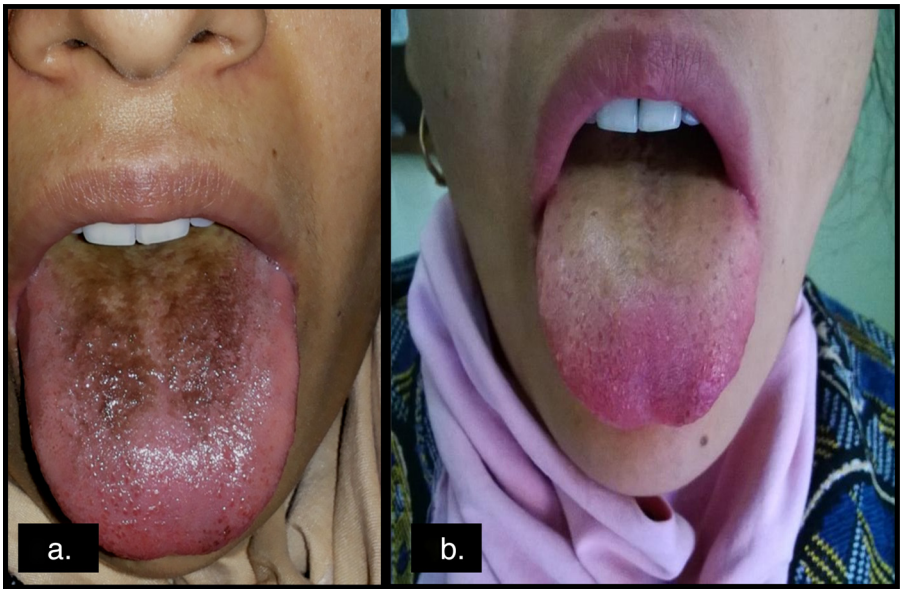

Fig. 2 – (a) Black hairy tongue in case 2 taking linezolid. (b) Normal tongue after withdrawal of linezolid.

4. Discussion

Linezolid was approved for clinical use in United States in April 2007 for methicillin resistant *Staphylococcus aureus* and vancomycin-resistant *Enterococci*. Additional case reports have documented some efficacy in the management of tuberculosis, Infective endocarditis, nocardiosis and in anaerobic infections. Linezolid is classified as group 5 drug for the management of DRTB by WHO. Serious neuropathy (both optical and peripheral) has been reported in patients receiving therapy for more than 28 days.[8]

BHT, or lingua villosanigra, presents as a black coating on the tongue's dorsum, anterior to the circumvallate papillae. Usually it does not affect the tip or the sides of the tongue. BHT is a self-limiting disorder characterized by abnormal hypertrophy and elongation of filiform papillae on the surface of the tongue.[9] Most often asymptomatic, its principal associated problem is of esthetic order. The diagnosis of BHT relies on the visual identification of discolored, elongated, and hypertrophied filiform papillae. In both our cases BHT developed 2 weeks after starting the linezolid. Using the Naranjo's Adverse Drug Reaction Probability Scale, probability score was 6 for both the cases of probable linezolid induced BHT.

The etiology is unclear, but the disorder has been associated with numerous predisposing conditions. These include alcohol abuse, a history of smoking, or chewing tobacco, poor oral hygiene, after radiation therapy, poor feeding, smoking crack cocaine or other street drugs, using peroxide-containing mouthwash, radiation therapy, trigeminal neuralgia, using drugs that cause xerostomia like anticholinergics, antihypertensives and antidepressants like olanzapine, and antibiotics such as bismuth, tetracyclines, penicillins, linezolid.[10,11] Both our patients were non-smoker with no history of alcohol abuse or any other medication.

BHT is usually cured by discontinuation of the offending agent, a variety of measures, particularly cleaning of the tongue with a soft toothbrush and a solution of 3% hydrogen peroxide or baking soda, may aid in resolution.[8] In both our patients the tongue cleared of discoloration after withholding linezolid. With counseling for good oral hygiene both the patients completed the 2 years course of linezolid 600 mg once a day along with other anti tubercular drugs without any recurrence.

5. Conclusion

Linezolid has evolved as a very important drug in management of MDR and XDR-TB and classified as group 5 drug for treatment of tuberculosis by WHO. It is used for long duration up to 2 years in the management of drug resistant tuberculosis. Brown-black and hairy tongue is a rare side effect of linezolid. In both of our cases this was transient and discoloration resolved after stopping the drug. The drug was safely reintroduced with counseling to perform good oral hygiene.

Conflicts of interest

The authors have none to declare.

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Case Report

Two cases of eyelid tuberculosis – An uncommon presentation of ocular tuberculosis

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ABSTRACT

Mycobacterium tuberculosis apart from being the causative agent of pulmonary tuberculosis is also notorious to cause tuberculosis at various sites in the human body and ocular tuberculosis is one of the extra pulmonary manifestations of this organism. The most common presentation of ocular tuberculosis is anterior uveitis or choroiditis caused by hematogenous infection or hypersensitivity after another organ infection. Eyelid involvement by tuberculosis is most of the times secondary to orbital involvement and often seen in the form of drainage sinus. Isolated eyelid tuberculosis is however uncommon. Here we report two such cases of eyelid tuberculosis in different age groups; first case in a young female and second case of an old aged female with different presentation. Fortunately both of them responded well to the antitubercular treatment.

1. Introduction

Mycobacterium tuberculosis has a large spectrum of extra pulmonary manifestations and ocular tuberculosis is one of them, pertaining to ocular tuberculosis the incidence of ophthalmic manifestations in patients known to have systemic manifestations is only 1–2%.[1] The most common presentation of ocular tuberculosis is anterior uveitis or choroiditis[2] caused by hematogenous infection or a hypersensitivity after another organ infection. Eyelid tuberculosis is a relatively uncommon presentation of ocular tuberculosis which can be primary or secondary[3,4] with the primary type being the unusual one out of the two. Eyelid involvement by tuberculosis is most of the times secondary to orbital involvement and often seen in the form of drainage sinus.

2. Case 1

A 20-year-old female patient presented to the departmental out patient department (OPD) with complaints of swelling over

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right eyelid around 3–4 months, the swelling was relatively painless and no other constitutional symptoms were present. There was no restriction of ocular movements. The intra ocular pressure was normal in both the eyes. Left eye and eyelid were normal. Patient had no past history of tuberculosis or any other significant ailment. She was primarily anxious as the swelling was giving an impression of cosmetic disfigurement. She was advised routine investigations including hemogram, blood sugar, chest X-ray and Mantoux test. Patient was subjected to histopathology from eyelid swelling. On reviewing the investigations, not to our surprise, the patient's histopathology was suggestive of granuloma formation comprising of epithelioid cells, Langhans giant cells and lymphocytes. All these findings suggested tubercular etiology and it was supported by positive Mantoux of 15 mm induration. Rest of the investigations was within normal limits. The patient was started on anti-tubercular chemotherapy comprising of Rifampicin (R), Isoniazid (H), Ethambutol (E) and Pyrazinamide (Z) according to body weight and was asked for follow-up visit after 2 months or earlier in case she has any problem. The patient was followed and was given treatment for almost 9 months with complete disappearance of the eyelid lesion (Fig. 1).

2.1. *Investigations*

Hemogram and blood sugar	Hb – 11.6 g/dl, TLC – 9000/cu/mm, DLC: N – 63, L – 33, M – 02, E – 02, random blood sugar – 84 mg%
Kidney function tests	Blood urea – 23.5 mg/dl, serum creatinine – 0.8 mg/dl
Liver function tests	Serum bilirubin (total – 0.5 mg/dl, direct – 0.3 mg/dl, indirect – 0.2 mg/dl) SGOT – 46 IU/L, SGPT – 76 IU/L, SALP – 312 IU/L

3. Case 2

A 61-year-old female presented to the OPD with complaints of pus discharge from a painful swelling over the eyelid on the right side and sensation of heaviness and difficulty in opening the right eye; however, there were no complaints regarding her vision. On examination the swelling was having an inflamed and edematous appearance diffusely involving the whole eyelid, tender on touch with a discharging sinus on the lateral aspect. On ophthalmological evaluation there was no restriction of ocular movements, the intra ocular pressure was normal in both the eyes. Left eye and eyelid were normal. The patient was given symptomatic and supportive treatment and was advised pus smear and culture for acid fast bacilli, Mantoux test apart from other routine investigations. Patient reported back with smear positive report of acid fast bacilli with Mantoux test positivity with induration of 11 mm and was subsequently started on four drug anti tubercular therapy (ATT) comprising of Rifampicin (R), Isoniazid (H), Ethambutol (E) and Pyrazinamide (Z) according to body weight but the patient came back after 4–5 days with complaints of ATT intolerance and gastric symptoms. ATT was stopped and she was advised liver function test (LFT) and routine investigations. Her LFT came out to be in normal limits. She was then introduced Isoniazid and Ethambutol along with omeprazole. After few days Rifampicin and Pyrazinamide were subsequently introduced one after the other with careful escalation of doses. This time she tolerated the regimen and then Pyrazinamide was stopped after around two and a half months and rest of the regimen was continued for around seven more months. The swelling almost disappeared with a small residual nodule (Fig. 2).

3.1. *Investigations*

Hemogram and blood sugar	Hb – 10.4 g/dl, TLC – 8000/cu/mm, DLC: N – 64, L – 32, M – 02, E – 02, random blood sugar – 96 mg%
Kidney function tests	Blood urea – 22 mg/dl, serum creatinine – 0.9 mg/dl
Liver function tests	Serum bilirubin (total – 0.6 mg/dl, direct – 0.4 mg/dl, indirect – 0.2 mg/dl) SGOT – 44 IU/L, SGPT – 72 IU/L, SALP – 344 IU/L

4. Discussion

Ocular tuberculosis was initially reported by Maitrejan in 1771.[5] Gueneau de Mussy reported choroidal tuberculoma in Miliary tuberculosis in 1830.[6] Ocular tuberculosis encompasses any infection by *M. tuberculosis* or related species viz. africanum, bovis and microti in on or around the eyes.[7] Primary ocular T.B. is devoid of any other systemic lesions but secondary Ocular T.B. results from infection from adjacent

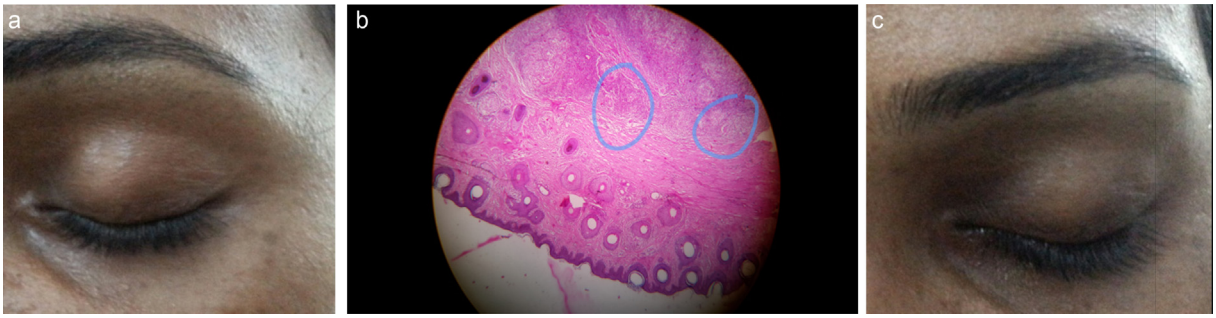

Fig. 1 – Case 1: (a) Before treatment. (b) H&E stained slide s/o granuloma formation 3. (c) After treatment.

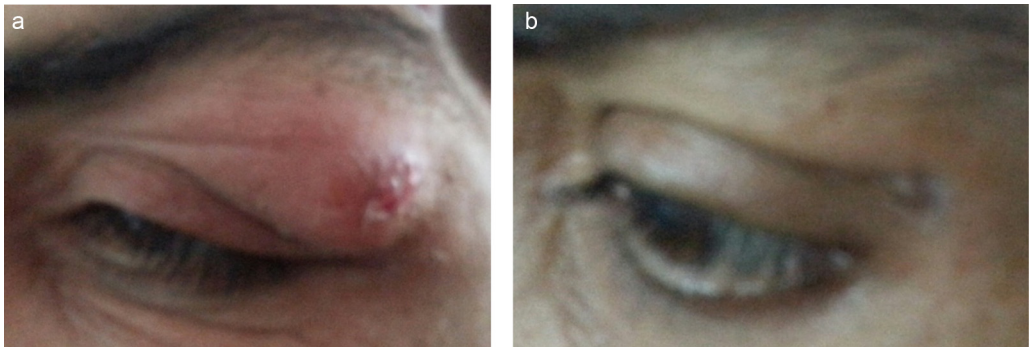

Fig. 2 – Case 2: (a) Before treatment. (b) After treatment.

contagious structures or by hematogenous spread. The commonly seen presentation of ocular T.B. are progressive unilateral proptosis, a cold, painless eyelid swelling, chemosis and conjunctival hyperemia. Involvement of ocular movements or loss of visual acuity can also be found in some cases. Eyelid involvement by tuberculosis is most of the times secondary to orbital involvement and often seen in the form of drainage sinus, scarring of the eyelids may lead to cicatricial ectropion, lagophthalmos or adhesion of eyelid structures to the underlying orbital bones, isolated involvement without orbital or systemic involvement is extremely uncommon.[4,8] Eyelid swelling needs to be differentiated from a stye or chalazion. Diagnosis is sometimes difficult and presumptive treatment on the basis of clinical features may be given in the absence of histological and microbiological evidence. The use of tuberculin test has certain limitations owing to its low sensitivity and specificity or sometimes incorrectly administered. Use of Polymerase Chain Reaction can be employed for DNA amplification[9] however the growth of the organism from the lesion remains the gold standard to establish the diagnosis. Ocular tuberculosis usually occurs in apparently healthy individuals who usually show evidence of inactive lesions. Involvement is mostly unilateral. Like pulmonary and other extra pulmonary tuberculosis treatment for ocular tuberculosis is similar and is effective if timely diagnosis is established and the stage of complications is not reached.

Conflicts of interest

The authors have none to declare.

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Case Report

A lengthy primary intramedullary tuberculoma of the spinal cord extending from C4 to D8: A case report

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ABSTRACT

Spinal intramedullary tuberculoma is a rare cause of spinal cord compression. We report a case that had an intramedullary spinal cord tuberculomas where the diagnosis was made by MRI and biopsy. The clinical presentation was that of a cord compression in a 30-year-old male febrile patient. This case of intramedullary spinal tuberculoma with a longitudinally extending lesion of the cervicothoracic spine from C4 to D8 is presented for the rarity of its presentation.

1. Background

This case of intramedullary spinal tuberculoma (IMST) with a longitudinally extending lesion of the cervicothoracic spine from C4 to D8 is presented for the rarity of its presentation. Generally, IMST occur usually in young people and most commonly involve the thoracic spinal cord.[1] The most common site of involvement was dorsal cord followed by cervical, cervicodorsal, and dorsolumbar regions.[2,3] Spinal cord compression can be due to various causes, but IMST is a rare cause. In this case of IMST, the diagnosis was confirmed by radiological, cerebrospinal fluid analysis, and by biopsy.

2. Case report

A 30-year-old male, HIV-negative patient presented with acute onset of benumbed sensation from the level of mid thorax with history of tight band-like constricting sensation over mid thorax with shock-like radiating pain over the lower back since more than 45 days with history of stiffness of both the lower limbs. The patient developed progressive weakness of both lower limbs with tripping of toes and spasms of both lower limbs over a period of 45 days with bladder disturbances. The patient had low-grade fever for last 2 months with evening rise of temperature.

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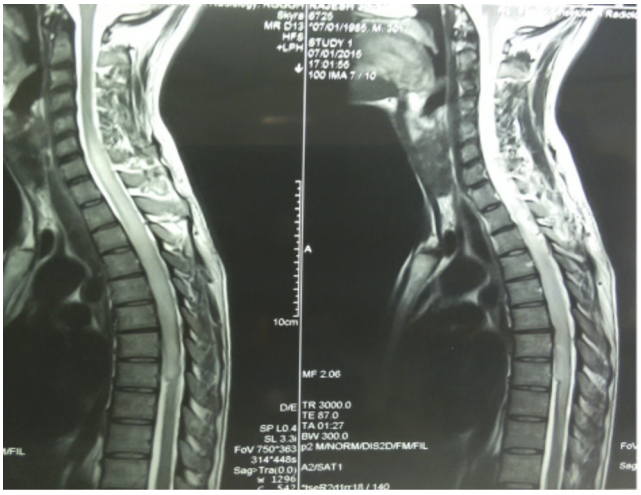

Image 1 – MRI showed cord expansion with T2 hyperintensity noted from level C4–D8.

On examination, the patient was afebrile vitals were normal. Cardiovascular, respiratory, and abdominal examinations were normal. The patients' higher mental function examination was normal and had no meningeal signs. The cranial nerves and fundus were normal. The tone was increased in both lower limbs with a pyramidal pattern of weakness in both lower limbs with exaggerated deep tendon reflexes from the C5 level with bilateral plantar extensor and absent superficial reflexes. All modalities of sensation were reduced below D4 level.

The blood investigations were done the complete blood count, and renal and liver function test serum B 12 levels were normal. The patient had a positive mantoux (15 mm). CSF analysis showed elevated protein 750 mg, sugar 88, the cell count was nil, and gram stain-negative and oligoclonal band were negative. MRI was done and found to have a cord expansion with T2 hyperintensity noted from level C4 to D8 (Images 1–3). The T2WI signal was weak in most of the central part and had enhanced margins in a rim shape. A collarette-like weak signal could be observed in the exterior margin, with sharp margins and ''target sign'' change. In addition the lesion showed intense homogeneous enhancement on contrast from lower D4 to D8 and on MRS showed a lipid peak.

In addition to anti-TB treatment, the patient underwent a C6-D8 decompressive laminectomy with midline myelotomy and excision biopsy of the lesion. On histopathology, the tissue biopsied showed extensive areas of caseation necrosis with scattered population of epithelioid histiocytes, lymphocytes, plasma cells, and few neutrophils suggestive of tuberculous pathology.

3. Discussion

The spinal tuberculosis constitutes a very common form of nonpulmonary tuberculosis and by far the most common granulomatous spinal infection. The first case of IMST was reported in 1828 by Albercombie.[1] Generally, most of the

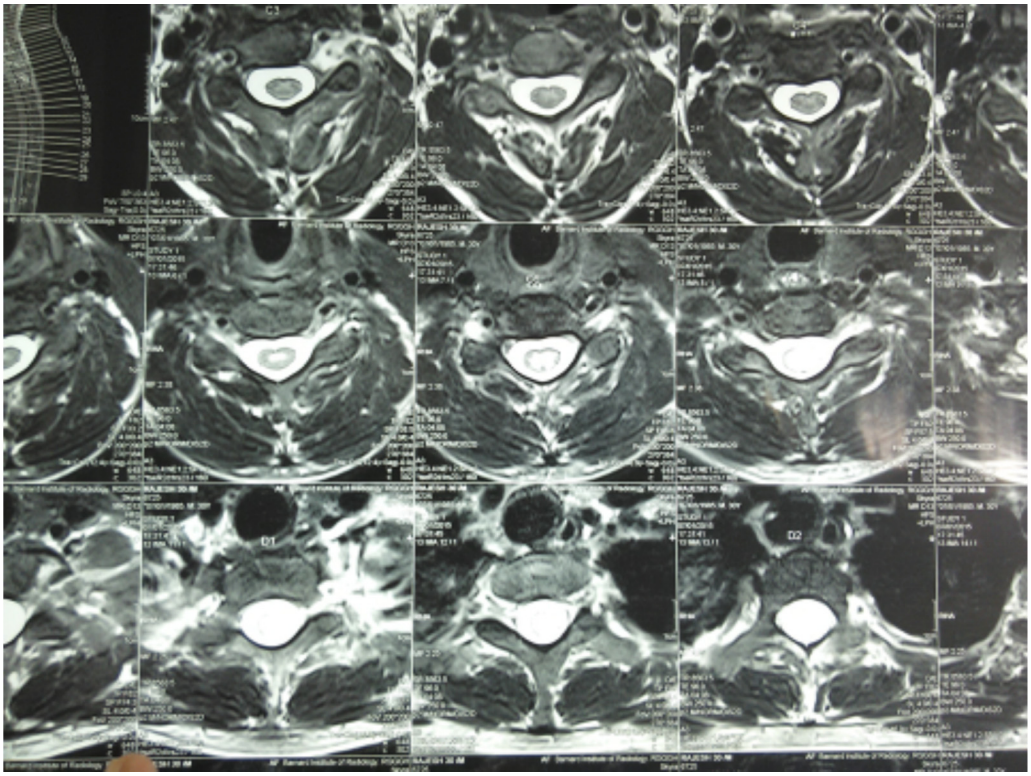

Image 2 – IMST had characteristic 'Target sign'.

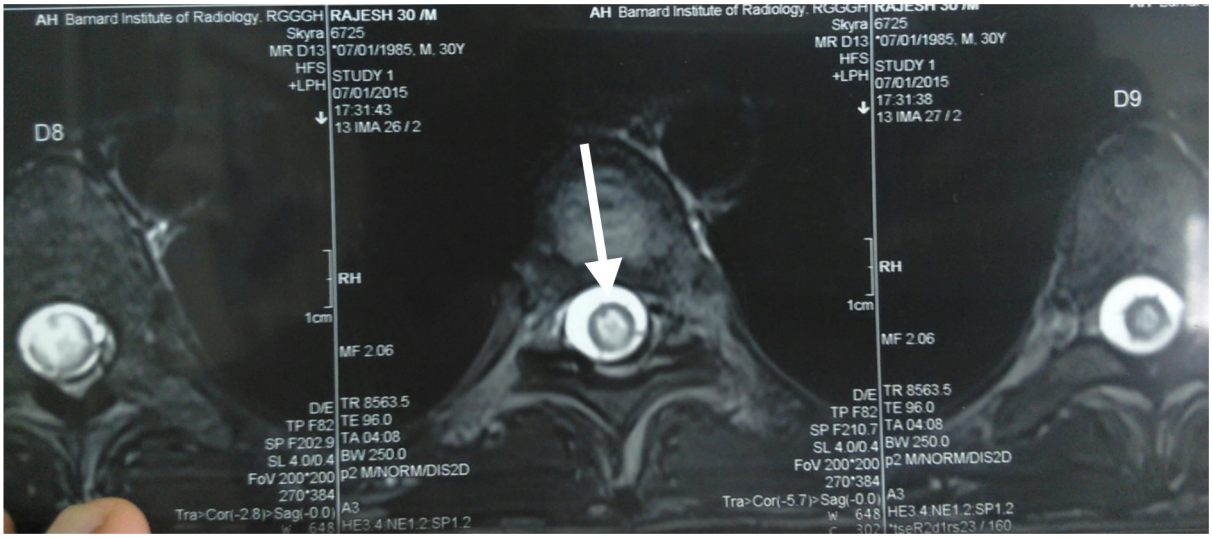

Image 3 – MRI showing 'Target sign'.

lesions are located in the thoracic cord, accounting for about 72% at the cervical level.

The lesion in our patient was at the level of the cervicodorsal region, which was similar to the other studies by Gupta et al., where they noted it to be most common in the younger people at the thoracic level. This is the first time that such a lengthy IMST lesion extending over 12 vertebrae is presented. Our patient had presented with the clinical picture suggestive of subacute transverse myelitis. The varied presentations reported in the other studies of IMST were signs of subacute spinal cord compression, Brown-Sequard syndrome, paraplegia,[4] and tuberculous abcess,[5] more commonly seen in immune-compromised patients with HIV, autoimmune diseases like systemic lupus erythematosus, patients on immune-suppressive treatment, and miliary tuberculosis.[6,7] Gupta et al.[8] presented eight cases of IMST, but only one of these cases was confirmed by open biopsy sampling and pathological examination.

IMST is mostly induced by hematogenous dissemination or cerebrospinal fluid infection; however, in a few cases, it is also observed to be caused by local spread from spinal tuberculosis.

On imaging, IMST has characteristic finding of a 'Target sign'. As caseation develops, the T2WI shows a typical 'target sign'. It exhibits a range from the low signal target to the high signal rim and also from the center of the low signal rim to the peripheral parts.[8–10] The high signal rim is due to the peripheral infective granulation tissue and the caseous substance forms the target center. The low signal rim in the external region is composed of collagen fibers produced by fibroblasts. The low signal rim may be incomplete or absent as the contents of the collagen fibers vary. The ''target sign'' is a valuable indicator that helps to differentiate spinal tuberculoma from other intramedullary lesions.

IMST can simulate various other intramedullary lesions. The other conditions with similar presentations include the common spinal intramedullary tumors, such as astrocytic glioma, ependymocytoma, and hemangioblastoma.

4. Conclusion

Intramedullary tuberculomas of spinal cord are rare. Gadolinium-enhanced MRI and biopsy from the tissue help in the accurate diagnosis of intramedullary tuberculoma. MRI also helps in monitoring the response to treatment and in further follow-up of these patients. IMST evaluated and diagnosed at an early stage has better prognosis. When started on antituberculous treatment, early medical treatment alone is sufficient. Surgery may be indicated for large lesions with rapid deterioration of the neurological status or when there is paradoxical increase in the size of the lesion following antituberculous treatment.

Conflicts of interest

The authors have none to declare.

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Original Article

Tuberculosis 'The Great Imitator': A usual disease with unusual presentations

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ABSTRACT

Background: A number of infectious diseases have been referred to by the phrase 'The Great Imitator', of which the oldest is syphilis; others include Lyme disease, nocardiosis, etc. Tuberculosis has been described as the second great imitator as it can imitate various other disease processes. An awareness of the atypical clinical manifestations of tuberculosis is important, especially in regions where tuberculosis continues to be a major public health problem, such as India. Extrapulmonary tuberculosis (EPTB) constitutes about 15–20% of all cases of tuberculosis in immunocompetent patients and accounts for more than 50% of the cases in human immunodeficiency virus (HIV)-positive individuals.

Methods: We hereby report 4 cases of tuberculosis at unusual sites, which were not suspected clinically and were subsequently diagnosed by pathological examination and by ancillary techniques.

Observations and results: In all the four cases, the involvement was extrapulmonary in nature and at unusual sites. Three cases were diagnosed by a positive Ziehl Neelsen stain while culture for Mycobacterium tuberculosis was positive in three cases. All the four patients tested negative for HIV status on serology.

Conclusions and implications: Unusual presentations, which mimic many diverse conditions, as seen in this series, highlight the importance of a high index of suspicion in the timely diagnosis of tuberculosis. Evidence of systemic or lung involvement may not always be present and laboratory and radiological findings play an important role.

1. Introduction

'The Great Imitator' is a phrase used for medical conditions with a nonspecific symptomatology which can be easily confused with a number of other diseases. A number of infectious diseases have been referred to by this phrase, of which the oldest is syphilis. It has long been known that syphilis with its varied and diverse presentations often mimics many other diseases.[1] A newer disease caused by the

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spirochete Borrelia burgdorferi, Lyme disease, which was named after the Connecticut town where it was first identified in 1975, has also been called the great imitator. Symptoms of chronic Lyme disease mirror those of many other ailments, including ordinary flu, multiple sclerosis, and brain tumors.[2] Nocardia spp. are ubiquitous environmental saprophytes. Nocardiosis may be a life-threatening infection in solid-organ transplant patients. Due to a variety of clinical presentations, nocardiosis has been named as the great imitator in solid organ transplants.[3] Maurice L. Sievers described tuberculosis as the Second Great Imitator and stressed that tuberculosis can also imitate various other disease processes.[4] An awareness of the atypical clinical manifestations of tuberculosis is important, especially in regions where tuberculosis continues to be a major public health problem, such as India. We hereby present 4 cases of tuberculosis at unusual sites, which were not suspected clinically and were subsequently diagnosed by pathological examination and by ancillary techniques.

2. Case 1

A 24-year-old female patient presented in the ENT Outpatient Department with lower lip swelling for past 25 days. The patient complained of loss of appetite and weight since the last few months. On enquiring, a history of contact was elicited, as her husband was a known case of tuberculosis who was diagnosed 3 years back. A history of irregular intake of anti-tubercular drugs was also obtained from him. Her general condition was stable, she was afebrile, and no cervical lymphadenopathy was noted. Local examination showed a swelling on the mucosal aspect of the lower lip which had a soft cystic consistency, measuring 1 cm × 1 cm in size and reddish blue in color (Fig. 1). A provisional clinical diagnosis of retention cyst was made and the patient was referred for fine needle aspiration cytology (FNAC) of the lip swelling. The FNAC smears showed moderate cellularity comprising of sheets of histiocytes along with neutrophils in a highly necrotic background. Many epithelioid cell granulomas and multinucleated giant cells were also evident. Ziehl Neelsen stain for acid fast bacilli was found to be positive. A cytological impression of tubercular abscess, lower lip was made. On culture, the aspirate was positive for Mycobacterium tuberculosis.

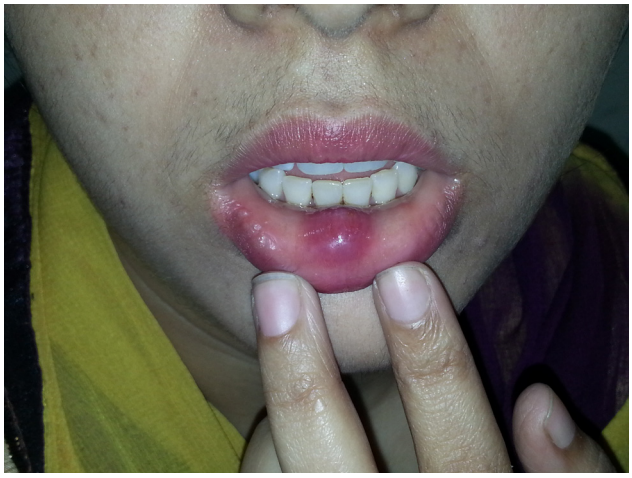

Fig. 1 – Photograph of cystic swelling lower lip diagnosed as tuberculous lesion on FNAC.

X-ray chest PA view showed a lobulated soft tissue opacity in the right hilum suggestive of lymphadenopathy and also small opacities in right upper lobe. Computerized tomographic (CT) scan thorax was also done and showed multiple enlarged, conglomerate, necrotic peripherally enhancing lymph nodes in right paratracheal, pretracheal, subcarinal, and right hilar locations. Few small discrete nodular opacities with surrounding ground glass haze were seen in the posterior segment of right upper lobe, subpleural in right base, apical segment of left lower lobe, and in left basal region. The radiological impression of an infective pathology, likely Koch's etiology was made. A standard combination treatment of four-drug regimen (anti-tuberculous treatment) was started, which resulted in symptomatic improvement in the patient and healing of the lesion. This case has been published as a case report.[5]

3. Case 2

A 16-year-old male presented to the surgical out-patient department with a painless scalp swelling and a discharging sinus in the occipital region. No history of seizures suggestive of neurological symptoms was elicited. On examination, the patient was afebrile, a soft, nontender, nonpulsatile scalp swelling measuring 3 cm × 2 cm was seen along with a discharging sinus, localized to the occipital region, and the possibility of epidermal cyst was considered. Routine chest roentgenogram (PA view) was normal. Radiograph of the skull was nonspecific, and erosion of the bone underlying the swelling was suspected. CT scan was advised; however, due to paucity of funds, the patient could not afford the investigation. Fine needle aspiration of the swelling yielded only necrotic debris with no viable cells.

Surgical intervention was indicated for diagnostic purposes and excision of the swelling with sinus along with bony debridement was done. Histopathological examination (HPE) of soft tissue and bony curettings revealed areas of necrosis, diffuse infiltration by polymorphs, and lymphoplasmacytic infiltrate. Presence of epitheloid cell granulomas with Langhan's giant cells and necrotic material was diagnostic (Fig. 2). Acid fast bacilli were demonstrated on Ziehl Neelsen staining, thereby confirming the diagnosis of tuberculosis. A definitive diagnosis of granulomatous lesion of tubercular etiology was made. The sample was also positive for Mycobacterium tuberculosis on culture.

The patient was managed accordingly and anti-tuberculosis therapy was started. The patient has since been in follow-up and has shown good clinical recovery. This case has been published as a case report.[6]

4. Case 3

A 30-year-old male reported to the ENT OPD with complaints of gradually increasing nasal stuffiness and obstruction since

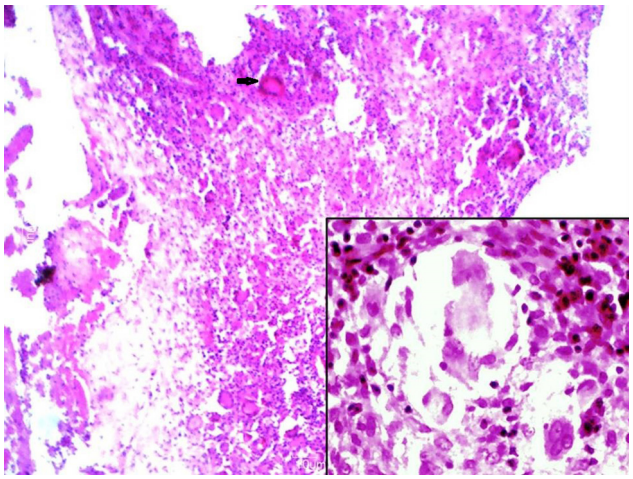

Fig. 2 – Microphotograph showing dead necrotic, granulation tissue, Langhan's giant cell (arrow) in a case of calvarial tuberculosis. Inset shows giant cell and lymphoplasmacytic infiltrate (H&E, 40×).

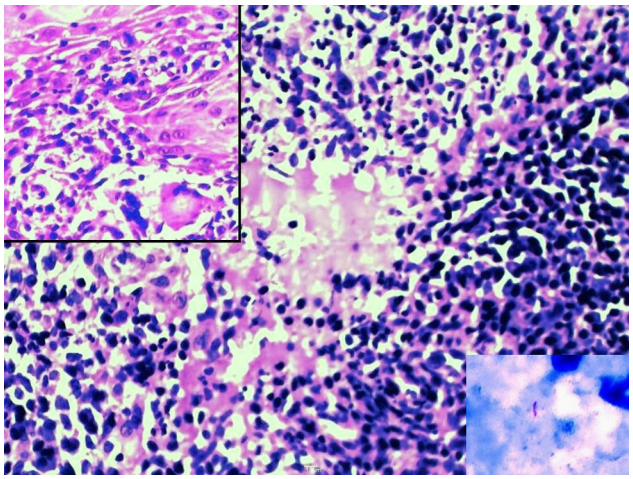

Fig. 3 – Section from nasal tuberculosis showing necrosis and lymphoplasmacytic infiltrate. Inset (top left corner) shows Langhan's giant cell just below epidermis (H&E, 40×); inset (bottom right corner) shows acid fast bacilli (Ziehl Neelsen Stain, 100×).

the last 6 months and 1 episode of epistaxis. He also gave complaints of watery rhinorrhea and postnasal drip since the last 1 week. Anterior and posterior rhinoscopy revealed multiple bilateral, pale gray polypoid masses arising from the middle meatus and prolapsing into the nasal cavity. A clinical impression of nasal polyposis leading to nasal obstruction was made. Plain X-ray of the paranasal sinuses showed only opacification; hence, a CT scan was advised which showed polyps as rounded bodies of soft tissue arising from the mucosal surfaces of nose and paranasal sinuses. These were clearly differentiated from the surrounding inflamed mucosal lining and nasal secretion, as they were more radio dense and brighter. The clinical diagnosis was of ethmiodal polyposis and the patient was taken up for polypectomy. Routine chest roentgenogram (PA view) was normal and no regional lymphadenopathy was noted. HPE of the excised polypoid tissue showed epitheloid cell granulomas with Langhan's giant cells with central caseation. A diffuse lymphoplasmacytic infiltrate with congested capillaries was seen in the background (Fig. 3). Acid fast bacilli were demonstrated on Ziehl Neelsen staining thereby confirming the diagnosis of tuberculosis. A definitive diagnosis of granulomatous lesion of tubercular etiology was made. The excised tissue was also sent for culture studies and tested positive for Mycobacterium tuberculosis. As per the existing guidelines, the patient was started on antitubercular medication. The treatment resulted in a rapid resolution of nasal blockade and the patient is now on regular follow-up.

5. Case 4

A 24-year-old male reported to the orthopedics OPD with complaints of swelling in the left leg. Ultrasonography revealed left popliteal baker's cyst and left gastrocnemius hypertrophy. This was followed by a Color Doppler which showed a fusiform, partially septated Baker's cyst in the left popliteal fossa. Musculotendinous hypertrophy of left gastrocnemius was noted and magnetic resonance imaging (MRI) of the left leg was advised. MRI showed muscle edema with swelling of gastrocnemius and to a lesser extent of the soleus muscle with overlying subcutaneous edema. The possibilities suggested were: (1) Hoffman's myopathy and (2) muscular dystrophy. Plain X-ray of the left lower leg and knee joint was normal. A routine chest X-ray showed prominent left hilar adenopathy. CT scan of the chest showed fibro-nodular opacities in apical segments of both upper lobes with mediastinal lymphadenopathy, which was suggestive of infective etiology. Thyroid function tests were done to rule out Hoffman's myopathy, and all values were within normal limits. A muscle biopsy of the hypertrophied gastrocnemius muscle was done. HPE revealed numerous epitheloid cell granulomas and Langhan's giant cells with central necrosis (Fig. 4). A widespread mononuclear cell infiltrate extending from the perimysium and between the muscle fibers was seen. Ziehl Neelsen stain for AFB was negative. The histopathological diagnosis was granulomatous lesion of left gastrocnemius of possible tubercular origin. The muscle biopsy tissue was subjected to GeneXpert MTB/RIF (Xpert) assay system and reported as positive for Mycobacterium tuberculosis. The patient was started on a regimen of four-drug antitubercular chemotherapy (2HREZ/4HR3). He has shown significant clinical improvement and is presently on regular follow-up.

A comparative summary of the salient features of these 4 cases is shown in Table 1.

6. Discussion

Tuberculosis continues to be a major cause of morbidity and mortality, especially in the developing world. With an estimated 9 million new cases and 2 million deaths every year, tuberculosis remains a leading public health problem worldwide.[7]

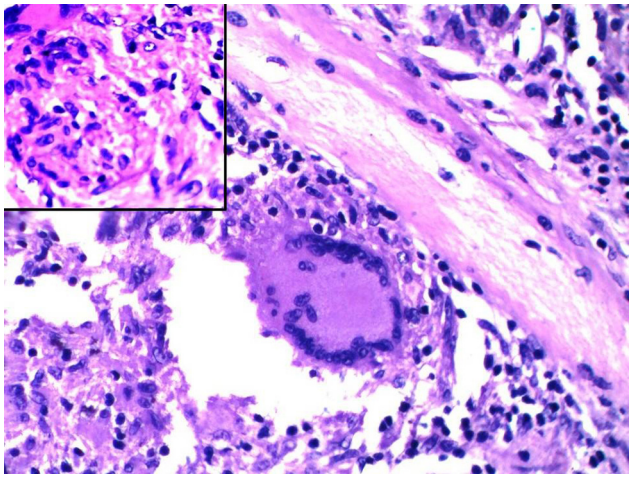

Fig. 4 – Sections showing Langhan's giant cell and epithelioid cell granulomas (inset) within muscle bundle (H&E, 40×).

Extrapulmonary involvement can occur in isolation or along with a pulmonary focus as is seen in disseminated tuberculosis. The recent human immunodeficiency virus (HIV) and acquired immunodeficiency syndrome (AIDS) pandemic has resulted in changing epidemiology, bringing extrapulmonary tuberculosis (EPTB) into the limelight. EPTB constitutes about 15–20% of all cases of tuberculosis in immunocompetent patients and accounts for more than 50% of the cases in HIV-positive individuals. Lymph nodes are the most common site of involvement followed by pleural effusion and virtually every site of the body can be affected.[8] Since the clinical presentation of EPTB is atypical, often tuberculosis is not suspected by the clinician, as was seen in all the four above cases. Sophisticated imaging techniques such as CT scan and MRI and procedures such as laparoscopy and endoscopy have tremendously helped in the anatomical localization of EPTB and also to obtain tissue for biopsies for a definitive diagnosis. The disease usually responds to standard antituberculosis drug treatment. In the present series, the involvement was extrapulmonary in nature and at unusual sites and all the four patients tested negative for HIV status on serology.

Oral tuberculosis is rare and accounts for less than 1% of all cases of tuberculosis. It is seldom primary, but more commonly secondary to pulmonary disease and the tuberculous lesion may precede the detection of pulmonary tuberculosis as was seen in the present case. It has been suggested that factors such as the presence of saprophytes, protective effect of saliva, resistance of striated muscle to bacterial invasion, and the thickness of protective epithelial covering contribute to the relative resistance of the oral cavity to tuberculosis.[9] The tongue, gingiva, and palate are the usual sites of involvement. In the tongue, the typical presentation is a nonhealing painful ulcer at lateral border or the tip of the tongue in which a differential diagnosis of simple traumatic ulcer and carcinoma is often considered.[10] The palate is another common site of involvement in the oral cavity, the hard palate being more frequently involved than the soft palate.[11] Among all these localizations in the oral cavity, tubercular involvement of the lip, as seen in Case 1, is even rarer. In the present case, the clinical presentation was also unusual, a cystic lesion was seen in the lower lip, and the first impression was a retention cyst. There were no enlarged cervical lymph nodes which also was an unexpected feature. Chauhan et al. have postulated that oral tuberculosis is usually acquired through infected sputum coughed out by a patient with open pulmonary tuberculosis or by hematogenous spread.[12]

Case 2 in this series presented with a scalp swelling and a discharging sinus and was diagnosed as calvarial tuberculosis on biopsy. Calvarial tuberculosis is recognized as a rare

Table 1 – Comparative summary of salient features of all the cases.

S. No	Age/sex	Clinical presentation	Clinical diagnosis	Diagnosis on cytology/ histopathology	Special/ancillary tests
Case 1	24 years female	Painless swelling lower lip	Retention cyst, lip	FNAC of the lip was compatible with tubercular abscess	Ziehl Neelsen stain for acid fast bacilli was positive, Culture for M Tb positive
Case 2	16 years male	Painless swelling in occipital region and discharge	Epidermal cyst, scalp	HPE of excised tissue along with the sinus and bony debridement was reported as granulomatous lesion of tubercular etiology	Ziehl Neelsen stain for acid fast bacilli was positive, Culture for M Tb positive
Case 3	30 years male	Nasal obstruction, epistaxis	Ethmoidal polyposes	HPE of excised polypoidal tissue was reported as granulomatous lesion of tubercular etiology	Ziehl Neelsen stain for acid fast bacilli was positive, Culture for M Tb positive
Case 4	24 years male	Painless swelling in calf	Hoffmans myopathy	HPE of muscle biopsy was reported as granulomatous lesion of tubercular etiology	GeneXpert MTB/RIF (Xpert) assay system positive for Mycobacterium tuberculosis

extra-pulmonary tuberculosis manifestation of tuberculosis. Involvement of the calvarium in tuberculosis is rare and even rarer is primary calvarial tuberculosis.[13] In the present case also, routine chest roentgenogram (PA view) did not reveal any pulmonary parenchymal lesion. CT scan of the head/thorax could not be done. Tuberculosis affecting bones account for 1% of all tuberculosis infections[14] and of these, only 0.2–1.3% comprise skull involvement.[15] This rarity may be attributed to deficiency of lymphatics in the calvarial bone, and thereby lack of spread from primary focus.[16] The definitive diagnosis of this unusual presentation of EPTB rests on the biopsy report and surgical debridement followed by anti-tubercular therapy is the mainstay of the management. Ramdurg et al. in a study of 21 cases of calvarial tuberculosis emphasized on the role of prompt surgical debridement and the importance of complete antitubercular drug therapy in the management of this rare disease.[17] Our patient also was managed with surgical debridement followed by institution of antitubercular therapy and showed a good clinical response.

Nasal tuberculosis was first described by Giovanni Morgagni in 1871 while conducting an autopsy on a young man with pulmonary tuberculosis with ulcerations of the nose, soft palate, and nasopharynx.[18] Tuberculosis of the nose, nasopharynx, and paranasal sinuses is known to be rare even in areas which are endemic for tuberculosis. It usually occurs either secondary to pulmonary tuberculosis or to lupus vulgaris of the facial skin with characteristic clinical presentation of local ulceration, crusting, bleeding, and advanced cases showing destruction of the nasal cartilaginous framework.[19,20] Our patient presented with bilateral nasal polyps which was unusual and the clinical impression was allergic ethmoidal polyposis. The presence of caseating granulomas, Langhan's type of giant cells in the excised polypoidal mass, and the demonstration of acid fast bacilli on special staining helped to clinch the diagnosis of nasal tuberculosis. Differential diagnosis in this clinical setting includes conditions like Wegener's granulomatosis, carcinoma, leprosy, sarcoidosis, subcutaneous phycomycosis, rhinoscleroma, rhinosporidium seebri, rhinitis sicca, etc.[21] Acid fast bacilli are at times not easily demonstrated in surgical specimens and Beltram et al. have suggested that the diagnosis of sino-nasal tuberculosis should be based upon (a) the absence of clinical response to empirical antibiotics and (b) the presence of caseous granulomatous inflammatory lesions on histopathology, and (c) identification of Mycobacterium tuberculosis in the surgical specimen.[22]

Musculoskeletal tuberculosis is a rare form of EPTB and has been reported to constitute 1–5% of all cases of tuberculosis.[23] Tuberculosis of soft tissue and muscle without underlying bony pathology is rare and there are very few reports in English literature of primary muscular tuberculosis without bony involvement or in immunocompetent patients.[24] Our patient, Case 4 was an unusual presentation of an immunocompetent young male in whom biopsy of the hypertrophied calf muscle confirmed tuberculosis, though the underlying long bone and knee joint were normal and chest imaging findings which were suggestive of tuberculosis. The rarity of skeletal muscle tuberculosis has been variously attributed to high lactic acid content of muscles, absence of reticuloendothelial or lymphatic tissue, rich blood supply, and the highly differentiated state of muscle tissue. However, none of these possibilities seem to be an adequate explanation.[25] Since the presentation is nonspecific and the clinical course is slow, diagnosis may be difficult unless there is a high index of suspicion. The possible differential diagnoses in such a clinical setting include intramuscular parasitic infections like cysticercosis or hydatid cyst, fungal infection, hematoma with secondary infection, pyomyositis, and soft tissue tumors such as myxoma, hemangioma.[26] The advent of DNA detection by PCR has helped to increase sensitivity of mycobacterial diagnosis and also allow for the exclusion of nontuberculous mycobacteria that can cause soft tissue infections.[27] In this case, the muscle biopsy tissue was subjected to GeneXpert MTB/RIF (Xpert) assay system and reported as positive for Mycobacterium tuberculosis.

7. Conclusion

Throughout the history of disease, tuberculosis has been universally acknowledged as a scourge with an unparalleled impact on mankind in terms of morbidity, mortality, and economic cost. Tuberculosis today is considered a re-emerging disease due to its increased incidence, particularly in immunocompromised patients. Unusual presentations of tuberculosis are increasingly being diagnosed and about one-fifth of all new cases of tuberculosis have an extrapulmonary lesion. Unusual presentations which mimic many diverse conditions, as seen in this series, highlight the importance of a high index of suspicion in the timely diagnosis of tuberculosis. Evidence of systemic or lung involvement may not always be present and laboratory and radiological findings play an important role. Definitive tissue diagnosis along with demonstration of AFB and isolation in cultures or by molecular techniques remains the gold standard.

Conflicts of interest

The authors have none to declare.

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Letter to the Editor

Need for species level identification of non-tuberculous mycobacteria in medical college laboratories in India

Medical colleges in India are part of the National Task Force (NTF) for tuberculosis and are diagnosing considerable number of TB patients. A National Level Workshop of Medical Colleges at All India Institute of Medical Science New Delhi in 2002 was instrumental in developing the structure and process required for the effective nation-wide participation of medical colleges in the Revised National Tuberculosis Control Programme (RNTCP).[1] Some of the medical colleges have even renovated their laboratories and are using newer diagnostic methods endorsed by WHO. While *Mycobacterium tuberculosis* (*M. tuberculosis*) remains the commonest organism causing disease in the developing world, including India, non-tuberculous mycobacteria (NTM) are also making their presence felt by causing mycobacterioses in both immunocompetent as well as immunocompromised hosts.[2–5] Even though the nontuberculous mycobacteria (NTM) have been known since a long time, the information across India is very patchy. There has not been a joint effort to know more about the diseases caused by these organisms, their pathogenesis and management, and there are no India-specific guidelines. Only a few groups like those from Central JALMA Institute for leprosy and other mycobacterial diseases, Agra; National Tuberculosis Institute, Bengaluru; National Institute for Research in Tuberculosis, Chennai; National Institute for Tuberculosis and Respiratory Diseases, New Delhi; Mahatma Gandhi Institute of Medical Science, Sevagram; All India Institute of Medical Science, New Delhi; Christian Medical College, Vellore; Post Graduate Institute of Medical Education and Research, Chandigarh; Hinduja Hospital, Mumbai; Lakshmi Vara Prasad Rao Eye Institute, Hyderabad; Sawai Man Singh Medical College, Jaipur; Government Medical College, Amritsar; Central Institute for Research on Goats, Mathura, etc. have been active at different time periods (Dr. VM Katoch, personal communication).

In a good mycobacteriology laboratory, mycobacteria are isolated in large numbers from both pulmonary and extra pulmonary specimens, and *M. tuberculosis* complex is easily differentiated from NTM using WHO prescribed tests such as slow rate of growth, niacin, catalase (drop method, tube semi quantitative method and heat stable catalase at 68 °C), nitrate test and growth on Lowenstein Jensen medium containing paranitro benzoic acid (PNB).[6] There are at least 170 species of mycobacteria; however, the number causing diseases in human beings is relatively small. Nonetheless, due to labour intensive nature of the tests, most laboratories shirk from performing the phenotypic tests for species identification. However, looking into the present scenario and their isolations in AIDS and immune-compromised patients, it is important to carry out not only species identification but also drug susceptibility testing. The phenotypic methods which can be carried out in routine laboratory include study of biological character of the isolate, biochemical reactions, high performance liquid chromatography (HPLC) or thin layer chromatography (TLC).[7] The genotypic methods include gene probes (AccuProbe™, Gen-Probe, San Diego, Calif or InnoLiPA Mycobacteria V2, Innogenetics NV, Ghent, Belgium), polymerase chain reaction followed by restriction analysis (PCR-RA) and PCR followed by gene sequencing e.g. 16S rRNA sequencing.[8,9]

Depending upon the scope and resources of the laboratory, all or some of the techniques are available and used for identification of NTM. Broadly speaking, the medical college laboratories still rely upon phenotypic identification methods, while the reference laboratories at the level of National Reference Laboratories (NRL) and Supranational Reference Laboratories (SNRL) utilise newer genotypic techniques. Today the medical college and Intermediate Reference Laboratories (IRLs) are relying upon the National Reference Laboratories (NRLs) for identification and speciation of NTM which increases the work load of NRLs. National Tuberculosis Institute Bangalore NRL is running a project for identification of NTM isolated from the states of Maharashtra, Rajasthan and Karnataka entitled ''Prevalence and speciation of non tuberculous mycobacterium under programmatic settings in India'' (personal communication with the Director NTI) and has requested other laboratories to submit their isolates to them so as to generate some data base.

We wish to share information regarding identification of 49 NTM isolates that were recovered in our medical college laboratory in central India as part of studies to isolate NTM from various clinical and environmental samples.[4,5] We relied on phenotypic as well as other methods for identification of both *M. tuberculosis* as well as NTM. NTM were isolated from various clinical (24 isolates) and environmental samples

(25 isolates). Phenotypic speciation was tried for all these isolates as described above using morphology and biochemical reactions. Following tests were used – temperature preference (°C), growth at 42 °C, growth at 52 °C, growth rate, pigment production in dark and on exposure to light, growth on PNB, growth on MacConkey, growth on 5% NaCl, niacin, semi-quantitative catalase (mm), heat stable catalase, nitrate reduction, tellurite reduction, tween 80 hydrolysis, aryl sulphatase 3 days, aryl sulphatase 14 days, urea hydrolysis, utilisation of citrate, mannitol, and inositol, iron uptake and pyrazinamidase.[5] There were 6 isolates out of 49 (24 clinical and 25 environment) that could not be identified by phenotypic methods.

In addition to phenotypic identification, the isolates were also sent to reference laboratories in India and abroad for confirmation following the national and international guidelines. As they were obtained at a different period of time, the isolates were sent to different laboratories – six isolates were sent to CDC Atlanta, USA, 14 to National TB Reference Laboratory, Bilthoven, the Netherlands and 34 isolates were sent to National JALMA Institute for Leprosy and other Mycobacterial Diseases (NJIL&OMD), Agra, India. There was overlapping of 5 isolates between Bilthoven and Agra. Different methods of identification were used in different laboratories – HPLC was used in the CDC, Atlanta, InnoLiPA V2 was used in the National TB Reference Laboratory, Bilthoven and PCR-followed by Restriction Analysis, and 16s rRNA sequencing was performed in JALMA, Agra.

Among the 24 clinical NTM isolates, the correlation between our laboratory and reference laboratory results was 75% (18/24) with 100% correlation for MAC (*M. avium*, $n = 12$) as well as *M. fortuitum* (2 isolates), while that for *M. simiae* it was only 50% (4/8). Two more isolates remained unidentified in our laboratory and were later identified as *M. wolisnkyi* and *M. vaccae* by the reference laboratory. For all the 25 environmental NTM isolates, the correlation was 100%. Four isolates were *M. avium*, while the rest belonged to rapidly growing mycobacterial species including *M. fortuitum* ($n = 11$), *M. chelonae* ($n = 3$), *M. abscessus* ($n = 3$), *M. flavescens* ($n = 2$), *M. phlei* ($n = 1$) and *M. thermoresistible* ($n = 1$).

Out of the 6 isolates, which could not be identified in our laboratory, as mentioned above 4 turned out to be *M. simiae* and one each was *M. vaccae* and *M. wolinskyi* as per the reference laboratory reports (Table 1). There were significant reasons for discrepancy. In case of *M. simiae*, though three isolates were photochromogens, their niacin test was negative, and other biochemical tests were inconclusive. Another isolate of *M. simiae* that could not be identified was also niacin negative but was wrongly classified as scotochromogen in the first instance. Moreover, none of the biochemical tests of these four isolates were suggestive of *M. simiae*.

M. simiae is a photochromogenic mycobacterium that grows on standard mycobacterial culture media without additional growth factors. It grows optimally at 37 °C, slowly at 25 °C and fails to grow at 40 °C and 20 °C. *M. simiae* isolates grow over the pH range 5.5–7.5, produce niacin, unlike other nontuberculous mycobacteria, are urease positive but lack phosphatase and nitrate reductase activities. One important observation made while processing the strains of *M. simiae* for PCR – Restriction Analysis of hsp 65 genes was about the restriction fragments obtained from amplified DNA after restriction with HaeIII and BstEII enzymes. The expected fragments, as per Telenti et al. (1993),[5] should have been 200 and 135 bp after HaeIII and 245 bp after BstEII. However, the observed fragments in these isolate were 145, 125 and 40 bp after restriction with HaeIII and 240, 125 and 80 bp after restriction with BstEII. These restriction patterns were the same as observed by Legrand et al. in 2000 in *M. simiae* isolates obtained from AIDS patients in the Caribbeans.[10]

One isolate which was finally identified by 16S rRNA sequencing as *M. vaccae*, also gave inconclusive results on phenotypic as well as genotypic methods (PCR-RA). Though its DNA was amplified, yet it gave restriction results which did not match any mycobacterial species. It also remained unidentified with InnoLiPA Mycobacteria V2, as the test did not have probe for this species.

The sixth isolate, *M. wolinskyi* had also remained unidentified in our laboratory. It could also not be identified on PCR-RA. For this organism the hsp65 gene amplified products when treated with HhaI and MspI restriction enzymes, give confirmatory results. As we had used HindIII and BstE2, it could not be identified by us on PCR-RA. It was finally identified by sequencing.

To conclude, 88% of the NTM isolates could be correctly identified by phenotypic tests in our laboratory. All the *M. avium*, the main clinical isolates, could be correctly identified. Gene sequencing proved to be the best method for identification, but is neither affordable nor easily accessible in all laboratories. It is thus recommended that the initial identification of mycobacterial isolates should be performed in the Routine Mycobacteriology laboratory of the medical colleges using phenotypic tests and if the strain remains unidentifiable, the help of reference laboratories should be sought. Although, there may be some discrepancy in the results obtained in various Reference Laboratories due to the test method used, but the magnitude is small. This will not only generate data at the local level but also greatly reduce the burden on NRLs which are already otherwise overburdened.

Table 1 – Identification technique used in reference laboratories for 6 discrepant isolates.

Mycobacterial species	Number of isolates	CDC Atlanta	National TB Reference Laboratory, Bilthoven	NJIL&OMD, Agra
M. simiae	2	HPLC	–	–
M. simiae	2	–	InnoLiPA Mycobacteria V2	PCR-RA & 16S rRNA sequencing
M. wolinskyi	1	–	–	16S rRNA sequencing
M. vaccae	1	–	Could not be identified using InnoLiPA Mycobacteria V2	16S rRNA sequencing

Recently, in a meeting held in Jaipur a progressive step has been taken by a small group of workers towards understanding the NTM by creating the Indian National Working Group on Nontuberculous Mycobacteria (INWG-NTM). It aims to bring the interested researchers, clinicians, epidemiologists and veterinarians on one platform to develop interim guidelines which can eventually become India specific final guidelines. More and more scientists working on NTM have been requested to join the group.

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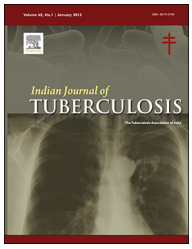

Letter to the Editor

Multidrug resistant tuberculosis during pregnancy

Dear Editor,

Multidrug-resistant tuberculosis (MDR-TB), a growing public health problem, disproportionately affects young adults, including women of childbearing age group.[1] With lack of experience in treating pregnant women with MDR-TB, some clinicians recommend medical termination of pregnancy (MTP) due to the fear of fetotoxicity while others recommend reducing or stopping treatment during pregnancy. A 25-year-old woman during her 12 weeks' of pregnancy was diagnosed with rifampicin resistant pulmonary tuberculosis with liquid culture showing sensitivity to isoniazid, ethambutol and streptomycin. As per PMDT guidelines of India which recommends MTP if the duration of pregnancy is <20 weeks in view of potential risk to the fetus, she was advised MTP.[2] However, due to lot of personal and social problems, she refused MTP. Hence after counseling and with expert consultations, she was started on modified MDR-TB regimen with injection streptomycin, isoniazid, ethambutol, pyrazinamide, cycloserine, PAS, moxifloxacin and pyridoxine at 16 weeks' of gestation. Obstetric scan revealed a single live intrauterine gestation corresponding to gestational age of 20–24 weeks with satisfactory fetal growth. With this regimen, she improved clinically with sputum conversion and at week 38, she delivered a live healthy female baby by Cesarean section. The neonate was not infected, was breast-fed and given 6 months of isoniazid preventive therapy followed by BCG vaccination.

This report shows that MDR-TB in pregnancy can be successfully treated without the need for MTP and good outcome for the baby emphasizing the need to rethink treatment strategy for MDR-TB in pregnancy. With careful monitoring and strong motivation, a positive outcome, for both the mother and the neonate, is possible with the use of second-line anti-TB drugs. MDR-TB patients found to be pregnant prior to treatment initiation or while on treatment should be evaluated, in consultation with an Obstetrician, for the severity of the disease against the risk and benefits of treatment. The management options for pregnant women with MDR-TB are few: stop or suspend TB treatment or terminate pregnancy. Here, this patient refused MTP though her sputum smears and cultures were strongly positive for MDR-TB. Treatment was clearly indicated not only to curtail her symptoms and weight loss but also to avoid dissemination, meningitis and death. Treatment also was required to terminate a possible source of transmission and to decrease the risk of congenital TB to the newborn. Hence holding or suspending treatment was inappropriate in this patient. Therefore we decided to offer her modified MDR-TB treatment after explaining to her the risk of such treatment. Favorable birth and treatment outcomes have been reported from other parts of the world.[3,4] Breast-feeding should be encouraged as long as the patient is sputum negative as the best way to prevent *M. tuberculosis* transmission to the newborn is the prompt initiation of ATT of the mother during both pregnancy and breastfeeding.[5] We think that women who become pregnant while being treated for MDR-TB should have an option to continue receiving treatment without termination of pregnancy. A mother should have the right to choose after understanding the merits and demerits of both options. We take this opportunity to point out the need to rethink on the advice for MTP for mothers with MDR-TB.

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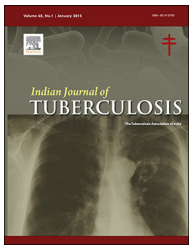

Abstracts

Angiopoietins as biomarkers of disease severity and bacterial burden in pulmonary tuberculosis

Kumar NP, Velayutham B, Nair D, Babu S. *Int J Tuberc Lung Dis* 2016; **21(1)**: 93–99. https://doi.org/10.5588/ijtld.16.0565

Background: Circulating angiogenic factors of the vascular endothelial growth factor family are important biomarkers of disease severity in pulmonary tuberculosis (PTB). However, the role of angiopoietins, which are also involved in angiogenesis, in PTB is not known.

Objective and design: To examine the association of circulating angiopoietins with TB disease or latent tuberculous infection (LTBI), we examined the systemic levels of angiopoietin (Ang) 1, Ang 2 and Tie-2 receptor in individuals with PTB ($n = 44$), LTBI ($n = 44$) or no tuberculous infection (NTBI) ($n = 44$).

Results: Circulating levels of Ang-1, Ang-2 and Tie-2 were significantly higher in PTB than in individuals with LTBI or NTBI. Moreover, Ang-1, Ang-2 and Tie-2 levels were significantly higher in PTB with bilateral disease. The levels of these factors also exhibited a significant positive relationship with bacterial burdens in PTB. Receiver operating characteristics curve analysis revealed Ang-2 as a marker distinguishing PTB from LTBI or NTBI. Finally, the circulating levels of Ang-1, Ang-2 and Tie-2 were significantly reduced following anti-tuberculosis chemotherapy.

Conclusions: Our data demonstrate that PTB is associated with elevated levels of circulating angiopoietins, possibly reflecting endothelial dysfunction. In addition, Ang-2 could prove useful as a biomarker to monitor disease severity, bacterial burden and therapeutic responses.

Conflicts of interest

The authors have none to declare.

Recent developments in genomics, bioinformatics and drug discovery to combat emerging drug-resistant tuberculosis

Swaminathan S, Sundaramurthi JC, Palaniappan AN, Narayanan S. *Tuberculosis* 2016; **101**. http://dx.doi.org/10.1016/j.tube.2016.08.002

Emergence of drug-resistant tuberculosis (DR-TB) is a big challenge in TB control. The delay in diagnosis of DR-TB leads to its increased transmission, and therefore prevalence. Recent developments in genomics have enabled whole genome sequencing (WGS) of *Mycobacterium tuberculosis (M. tuberculosis)* from 3-day-old liquid culture and directly from uncultured sputa, while new bioinformatics tools facilitate to determine DR mutations rapidly from the resulting sequences. The present drug discovery and development pipeline is filled with candidate drugs which have shown efficacy against DR-TB. Furthermore, some of the FDA-approved drugs are being evaluated for repurposing, and this approach appears promising as several drugs are reported to enhance efficacy of the standard TB drugs, reduce drug tolerance, or modulate the host immune response to control the growth of intracellular *M. tuberculosis*. Recent developments in genomics and bioinformatics along with new drug discovery collectively have the potential to result in synergistic impact leading to the development of a rapid protocol to determine the drug resistance profile of the infecting strain so as to provide personalized medicine. Hence, in this review, we discuss recent developments in WGS, bioinformatics and drug discovery to perceive how they would transform the management of tuberculosis in a timely manner.

Conflicts of interest

The authors have none to declare.

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Identifying children with tuberculosis among household contacts in The Gambia

Egere U, Togun T, Sillah A, Mendy F, Otu J, Hoelscher M, Heinrich N, Hill PC, Kampmann B. *Int J Tuberc Lung Dis*. 2016;**21 (1)**:6–11. https://doi.org/10.5588/ijtld.16.0289

Setting: Greater Banjul Area of the Gambia.

Objectives: To identify co-prevalent tuberculosis (TB) among child contacts of adults with smear-positive TB.

Design: Child contacts aged <15 years in the immediate household and compound were prospectively enrolled and evaluated for TB disease using screening questionnaires and the tuberculin skin test (TST). Symptomatic and/or TST-positive (≤10 mm) contacts were further investigated.

Results: Of 4042 child contacts who underwent symptom screening and TST, 3339 (82.6%) were diagnosed as TB-exposed but not infected, 639 (15.8%) were latently infected and 64 (1.6%) had co-prevalent TB. Of the 64 TB cases, 50 (78.1%) were from within the immediate household of the index case, and 14 (21.9%) from within the same compound. Of the 27 asymptomatic but TST-positive children diagnosed with TB, 7 were microbiologically confirmed. The median age of the TB cases was 4.4 years (interquartile range 1.9–6.9); 53.1% were aged <5 years. Of the 4042 child contacts, 206 (5%) slept in the same bed as the index case; 28.1% of all TB cases occurred in this group. Symptom screening alone would have detected only 57.8% of the co-prevalent cases.

Conclusion: In our community setting, if contact tracing is restricted to symptom screening and immediate households only, nearly half of all co-prevalent TB disease in child contacts would be missed.

Conflicts of interest

The authors have none to declare.

Relationship between nutritional support and tuberculosis treatment outcomes in West Bengal, India

Samue B, Volkmann T, Cornelius S, Mukhopadhay S, Jose M, Mitra K, Kumar AMV, Oeltmann JE, Parija S, Prabhakaran AO, Moonan PK, Chadha VK. *Journal of Tuberculosis Research* 2016. https://doi.org/10.4236/jtr.2016.44023

Introduction: Poverty and poor nutrition are associated with the risk of developing tuberculosis (TB). Socioeconomic factors may interfere with anti-tuberculosis treatment compliance and its outcome. We examined whether providing nutritional support (monthly supply of rice and lentil beans) to TB patients who live below the poverty line was associated with TB treatment outcome.

Methods: This was a retrospective cohort study of sputum smear-positive pulmonary TB patients living below the poverty line (income of <$1.25 per day) registered for anti-tuberculosis treatment in two rural districts of West Bengal, India during 2012 to 2013. We compared treatment outcomes among patients who received nutritional support with those who did not. A log-binomial regression model was used to assess the relation between nutritional support and unsuccessful treatment outcome (loss-to-follow-up, treatment failure and death).

Results: Of 173 TB patients provided nutritional support, 15 (9%) had unsuccessful treatment outcomes, while 84 (21%) of the 400 not provided nutrition support had unsuccessful treatment outcomes ($p < 0.001$). After adjusting for age, sex and previous treatment, those who received nutritional support had a 50% reduced risk of unsuccessful treatment outcome than those who did not receive nutritional support (Relative Risk: 0.51; 95% Confidence Intervals: 0.30–0.86).

Conclusion: Under programmatic conditions, monthly rations of rice and lentils were associated with lower risk of unsuccessful treatment outcome among impoverished TB patients. Given the relatively small financial commitment needed per patient ($10 per patient per month), the national TB programme should consider scaling up nutritional support among TB patients living below the poverty line.

Conflicts of interest

The authors have none to declare.

Finding the right dose of rifampicin, and the right dose of optimism

Ruslami R, Menzies D. *The Lancet Infectious Diseases* 2017;**17 (1)**:2–3. http://dx.doi.org/10.1016/S1473-3099(16)30315-2

After the widespread introduction of rifampicin in the early 1970s, it took another two decades, and more than 50 randomised trials with more than 20,000 participants[1] to finalise the drugs, doses, and schedule for the currently recommended regimen for newly diagnosed patients with active tuberculosis. Yet this regimen has important drawbacks, most notably the 6 months duration, and frequent toxicity. These limitations have stimulated considerable research interest to find shorter and better-tolerated regimens.

New drug development is expensive, and progress in the past 20 years has been very slow. Investigators have re-examined current drugs and doses, including the dose of rifampicin, which was initially selected as the lowest effective dose because this drug was very expensive when first introduced. Bacterial clearance in mice,[2] extended early bactericidal activity in patients with pulmonary tuberculosis,[3] and 6-month survival in patients with tuberculosis meningitis[4] have all been improved with higher doses of rifampicin. In patients with tuberculosis, meningitis survival was closely related to serum concentrations.[5] In *The Lancet Infectious Diseases*, Martin Boeree and colleagues[6] report findings of a randomised controlled phase 2B trial of patients with drug-sensitive pulmonary tuberculosis. The trial assessed four experimental regimens given for 12 weeks followed by 14 weeks of isoniazid and rifampicin. The regimen with rifampicin dosage of 35 mg/kg (RIF_{35}) resulted in faster time to culture conversion compared with the standard regimen. This difference was not seen with the other experimental regimens (including two with rifampicin dose of 20 mg/kg), and was seen

only with liquid culture media, but not solid cultures. Compared with the standard regimen, serious adverse events including hepatitis were not significantly higher with any experimental regimen, although the study was underpowered for this outcome, and the occurrence of hepatitis with $RIF_{35}$was more than twice as high as with standard rifampicin doses.

There are two important methodological issues to consider when interpreting this interesting and well executed study; use of the innovative multi-arm, multi-stage (MAMS) design, and time to culture conversion as the primary outcome. The MAMS trial design has been used successfully in phase 2 cancer trials to select regimens for phase 3 trials, and to minimise enrolment to regimens with inadequate efficacy or excessive toxicity.[7,8] However, to successfully reduce the number of participants enrolled to worse regimens, the time from enrolment to outcome in participants included in the interim analyses must be substantially shorter than the total time to enrol all participants. In this trial, 117 participants were randomly assigned to the arms that were stopped early, compared with 127 randomly assigned to the experimental arms that were continued—the difference represented a 3% reduction of overall enrolment—a rather modest benefit.

The other consideration is the critical importance in phase 2 trials of the predictive accuracy of the intermediate outcome,[7] and a high negative predictive value is essential to avoid falsely concluding that a regimen is inadequate. In this trial, enrolment was stopped for two regimens containing SQ109, based on the time to culture conversion. But, before concluding that SQ109 should not be considered for phase 3 trials, what is the accuracy of this outcome? Using meta-regression techniques, Wallis and colleagues[9] found a relationship between 2-month culture conversion (a dichotomous outcome) and relapse. This spurred highly optimistic thinking about the value of phase 2b trials, since dampened by the failure of 4-month fluoroquinolone-containing regimens to achieve relapse free cure in three independent trials,[10–12] despite promising culture conversion data.[13,14] We advocate for continued study of SQ109, since Wallis and colleagues[9] did not estimate negative (or positive) predictive values, nor did they examine the relationship of relapse free cure with time to culture conversion, the outcome used in this trial.

We believe that a shorter regimen for active tuberculosis that is also safe and well tolerated is urgently needed. Phase 2 trials can be helpful to identify promising regimens, but the intermediate outcome of 2 or 3 months culture conversion requires further validation work, before we can confidently use this outcome to plan phase 3 trials. This work would also allow use of the more efficient MAMS design. Boeree and colleagues are very optimistic that high dose rifampicin might be useful in shortening current treatment for drug sensitive tuberculosis; we share their optimism, but in a more limited dose.

Conflicts of interest

The authors have none to declare.

Estimating the global burden of multidrug-resistant tuberculosis among prevalent cases of tuberculosis

Nourzad S, Jenkins HE, Milstein M, Mitnick CD. *Int J Tuberc Lung Dis.* 2016;**21(1)**:6–11. https://doi.org/10.5588/ijtld.16.0110

Background: Estimates of the multidrug-resistant tuberculosis (MDR-TB) burden are based on incomplete, infrequently updated data among a limited pool of notified or incident pulmonary TB cases.

Methods: Using World Health Organization data reported by 217 countries/territories in 2014, we calculated the MDR-TB burden among prevalent TB cases and compared these with estimates among incident and notified TB patients. We also compared treatment coverage across estimates.

Results: Among prevalent TB patients worldwide in 2014, we estimate that 555 545 (95% credible bounds 499 340–617 391) MDR-TB cases occurred. This is 85% more than the 300 000 estimated among notified cases, and 16% more than the 480 000 among incident cases. Only 20% of MDR-TB cases among prevalent—compared to 37% of MDR-TB among notified—TB patients had access to MDR-TB treatment. Applying prior estimates, only 10% of MDR-TB cases will have successful outcomes.

Conclusion: Estimates based on likely-to-be-diagnosed cases of MDR-TB overlook a significant proportion of morbidity, mortality, and transmission that occur in undiagnosed, untreated, prevalent TB patients. Even though it may still likely underestimate the true disease burden, MDR-TB among patients with prevalent TB represents a closer approximation of disease burden than currently reported indicators. Progress toward elimination or control depends on policies guided by a more complete representation of the disease burden.

Conflicts of interest

The authors have none to declare.

Detection and quantification of differentially culturable tubercle bacteria in sputum from patients with tuberculosis

Chengalroyen MD, Beukes GM, Gordhan BG, Streicher EM, Churchyard G, Hafner R, Warren R, Otwombe K, Martinson N, Kana BD. *American Journal of Respiratory and Critical Care Medicine* 2016; **194(12)**:1532–1540. http://dx.doi.org/10.1164/rccm.201604-0769OC

Rationale: Recent studies suggest that baseline tuberculous sputum comprises a mixture of routinely culturable and differentially culturable tubercle bacteria (DCTB). The latter seems to be drug tolerant and dependent on resuscitation-promoting factors (Rpfs).

Objectives: To further explore this, we assessed sputum from patients with tuberculosis for DCTB and studied the impact of exogenous culture filtrate (CF) supplementation *ex vivo*.

Methods: Sputum samples from adults with tuberculosis and HIV-1 and adults with no HIV-1 were used for most probable number (MPN) assays supplemented with CF and Rpf-deficient CF, to detect CF-dependent and Rpf-independent DCTB, respectively.

Measurements and main results: In 110 individuals, 19.1% harbored CF-dependent DCTB and no Rpf-independent DCTB. Furthermore, 11.8% yielded Rpf-independent DCTB with no CF-dependent DCTB. In addition, 53.6% displayed both CF-dependent and Rpf-independent DCTB, 1.8% carried CF-independent DCTB, and 13.6% had no DCTB. Sputum from individuals without HIV-1 yielded higher CF-supplemented MPN counts compared with counterparts with HIV-1. Furthermore, individuals with HIV-1 with CD4 counts greater than 200 cells/mm^3 displayed higher CF-supplemented MPN counts compared with participants with HIV-1 with CD4 counts less than 200 cells/mm^3. CF supplementation allowed for detection of mycobacteria in 34 patients with no culturable bacteria on solid media. Additionally, the use of CF enhanced detection of sputum smear–negative individuals.

Conclusions: These observations demonstrate a novel Rpf-independent DCTB population in sputum and reveal that reduced host immunity is associated with lower prevalence of CF-responsive bacteria. Quantification of DCTB in standard TB diagnosis would be beneficial because these organisms provide a putative biomarker to monitor treatment response and risk of disease recurrence.

Conflicts of interest

The authors have none to declare.