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Editorial

CHALLENGES IN DIAGNOSIS AND TREATMENT OF LATENT TUBERCULOSIS INFECTION

[*Indian J Tuberc 2012; 59:* 1 - 5]

Tuberculosis continues to dominate among infectious diseases globally due to its extreme contagious nature, ability to remain latent in the host for an indefinite period and then reappear later as an overt disease. One-third of world's population (approximately two billion) is estimated to be infected with *Mycobacterium tuberculosis*. The prevalence of latent tuberculosis infection (LTBI) in India ranges from 9-80% in various populations. This enormous pool of individuals poses a great hurdle for global tuberculosis control. Globally, around nine million people develop tuberculosis, out of which 1.3 million die every year.[1] Despite this tremendous global burden, case detection rate continues to be low.

Individuals with LTBI are non-infectious as they are only infected with *M. tuberculosis* and do not have the active disease. About 90% infected people suffer from LTBI. They are usually asymptomatic. On an average, life time risk of developing active tuberculosis in individuals with latent tuberculosis infection is 5 - 10%. This risk further increases in immuno-compromised patients, very young and old persons. HIV patients with latent tuberculosis infections have 10% risk of active disease per annum as compared to 10% lifetime risk in general population.[2,3] Identification and treatment of individuals with LTBI is important for effective tuberculosis control. Treatment reduces the risk of developing active disease by 90% and also cuts down the further transmission.

The pandemic of HIV has altered both the epidemiology of tuberculosis and the measures to control it. Incidence of tuberculosis in HIV infected patients is about 100 fold higher than that in general population. About 2.5 million people or 0.4% of adult population in India are HIV sero-positive and 50% of them may develop tuberculosis as opportunistic infection.[4] Targeted testing and treatment for LTBI is a component of tuberculosis control in many low incidence and high endemic countries. It requires active screening and treatment of selected high risk group for LTBI. In contrast, it is not routinely done in countries like India having high incidence and limited resources.

Till recently, tuberculin skin test (TST) has been an important tool to know about the individuals having LTBI but now an alternative has emerged in the form of T-cell based interferon gamma release assays (IGRA), a new generation of *in vitro* tests of cellular immunity. While TST reflects delayed hypersensitivity to mycobacterial antigen, IGRA is a laboratory test for lymphocyte recognization and response to *M. tuberculosis*. IGRA is preferable in BCG vaccinated individuals but it is costlier than TST, so it should be advised after proper evaluation of cost factor. These tests are also evaluated in the light of the history of exposure to drug sensitive and drug resistant cases. Centres for Disease Control (CDC) strongly recommends

LTBI testing for all newly diagnosed HIV infected patients.[5] Test can be repeated in patients whose CD4 lymphocyte count increases i.e >200 cells/µl. Annual tests are advisable for previously TST negative patients. However, clinical experience is limited in this setting. No data is available to determine which test is more reliable. Data are also limited regarding specificity and sensitivity of Quantiferon GOLD test and T-SPOT and there is no gold standard recommendation. Few studies have shown higher positive results with T-SPOT than other IGRAs. TST may lead to false negative results in HIV infected persons with immunosuppression. So, once presence of active disease is excluded, they should be subjected to TST testing as soon as possible because of more chances of false negativity as CD4 + T lymphocyte decline i.e < 200/ cumm.[6]

CDC also recommends TST based diagnosis of LTBI if it is > 10mm in high risk group, >15mm in non-high risk group and >5mm in HIV group without considering previous BCG vaccination. Serial testing may also show booster effect. This may lead to over-diagnosis of LTBI and overtreatment, thus exposing the patient to possible drug adverse reactions. On the other hand, leaving these LTBI patients without treatment may lead to development of active disease and potential risk of increased tuberculosis transmission. These tests are also recommended for health care workers to detect LTBI in staff attending on immuno-compromised patients in hospitals who are at high risk of developing active disease. In an Indian study, 50% of health care workers were positive by either TST or IFN-γ assay, and 31% were positive by both tests. The prevalence estimates of TST and IFN-γ assay positivity were comparable and the agreement between the both the tests was high.[7] These tests are also useful in persons who are homeless, prisoners or have recently travelled to endemic countries.

India is having the highest TB burden with estimated annual incidence of two million (1/5 of global burden) with the National ARTI of 1.5% and prevalence of three million. It is also the highest MDR-TB burden country with an annual incidence of 99,000 cases. XDR TB cases have also been reported.[8] More and more people having immuno-compromised status e.g. malignancy, HIV, diabetic patients etc., are being diagnosed. Diabetic case burden is also high and it has been named as Diabetic Hub. Due to advances in the diagnosing techniques, detection of malignancy patients is increasing, thus putting more patients on chemotherapy and exposing them to increased risk of tuberculosis.

The situation of LTBI in developed countries is different from that in developing countries. While in developed nations, it is the reactivation of old infection of remote past which acts as a reservoir of infectious pool for potential case but in developing countries it is caused by the close contact of high burden infectious cases. Thus treatment of LTBI is important for developed countries. But in developing countries, priority is given to treatment of new sputum positive cases. Diagnosis and treatment of LTBI will increase financial burden on already stretched health care system. Moreover, one time treatment/ chemoprophylaxis will not ensure complete eradication of infection and future treatment may be needed. Epidemiological impact will also not be much in high burden countries. Thus, rather giving treatment to all persons of suspected LTBI, it will be wise to treat target population and persons having specific indications like persons having reversible risk factor. Persons having irreversible risk factors may again need treatment for TB as life long therapy. Likewise children of < 2 years, close household contact of sputum positive pulmonary tuberculosis and HIV infected individuals should also be benefitted. Persons recently infected i.e recent tuberculosis converter (increase in tuberculin reading > 10 mm within two years for age < 35 years and > 15mm for age > 35 years),

in whom risk of TB is great during initial two years are also a good candidate for treatment. All children of age < 5 years having tuberculin skin conversion should be covered as they are potential candidate for development of severe and fatal disease. Even tuberculin positive persons with stable radiographic findings suggestive of tuberculosis should be offered treatment after excluding active TB which requires full course of treatment. In low endemic settings and in developed countries, foreign based persons from high tuberculosis endemic area, medically under-served, low income group, high risk racial and ethnic group may also be treated with chemoprophylaxis of LTBI. It is also important to select patients who need full treatment or only chemoprophylaxis. An asymptomatic person with normal chest radiograph with positive TST/ IGRA should be offered treatment of LTBI. Isoniazid (INH) therapy is the best choice treatment for LTBI in drug sensitive cases. However, if the person is Isoniazid-resistant, then Rifampicin is used as alternate therapy. Isoniazid prophylaxis has shown to cut down incidence of disease by 80 % in first year. Though this protective effect wanes in subsequent years, but overall it helps to reduce the incidence of tuberculosis by approximately 50%.[9]

Isoniazid (INH) can be given in usual daily dose of 300 mg/day for nine months in adults or 270 doses within 12 months or given biweekly in high dose of 900 mg/day for nine months or 76 doses within 12 months. Rifampicin (RMP) is given 600mg daily for four months or 120 doses in six month.[10] For LTBI in a person exposed to MDR-TB, no reliable data on use of various regimens are available. Various options like six months Ethambutol (EMB) + Pyrazinamide (PZA) or Pyrazinamide + Fluoroquinolone has been given but their achieved success rate is not well-defined. So, these MDR-TB contacts are diagnosed and treated as per RNTCP guidelines of treatment of MDR-TB cases. Both Isoniazid and Rifampicin are prone to cause hepatotoxicity, so should be used with caution. Poor compliance may also be expected due to long duration of treatment i.e nine to 12 months. Drugs in combination (RMP + PZA) and (INH + RMP) for two to three months have given good success rate. This will also overcome primary resistance and therefore more suitable in India.

However, treatment of LTBI is full of difficulties and challenges. Major challenge is low rates of treatment initiation and completion. In various studies, it was found that only 32-63% persons could initiate therapy and out of them, 21-51% completed the treatment. Since potential severe toxicities are associated with the treatment of LTBI, this necessitates the monitoring specially in persons at increased risk of toxicity.[11-13] Low treatment initiation and completion rate can result in continued transmission of tuberculosis and additional burden of cases. Since they result from a lack of understanding on the part of patient, absence of symptoms, toxicity of the regimens and longer duration of treatment, efforts must be made to educate the patients regarding the importance of such therapy, particularly to the persons at higher risk. However, such therapy may add to additional cost and financial burden, specially in high endemic areas and limited resources.

The bigger challenge is the need for short course treatment of LTBI, though newer drug trials like Isoniazid with Rifapentine or combination chemotherapy with Moxifloxacin have shown promising results but still large multi-centric trials are needed to further support the effectiveness.[14,15]

In a recent study in Africa, it has been found that primary isoniazid prophylaxis did not improve tuberculosis-disease–free survival among HIV-infected children or tuberculosis-infection–free survival among HIV-uninfected children immunized with BCG vaccine. Despite access to antiretroviral therapy, the burden of tuberculosis remained high among HIV-infected children.[16] Another study by Martinson *et al*[17] was a more

conventional comparison of four secondary prophylaxis regimens among persons with tuberculosis and HIV infection in a high-risk South African setting. The new regimens of rifapentine–isoniazid weekly for three months, rifampin–isoniazid twice weekly for three months, and continuous isoniazid therapy for up to six years were compared with six months of conventional therapy. All the four regimens were found to be effective, but the rates of active tuberculosis or death were no different from the two new, supervised, rifamycin-containing regimens than with the conventional 6-month isoniazid regimen. However, in a post hoc, as-treated analysis, patients in the continuous-isoniazid group had a 58% lower rate of tuberculosis or death than those receiving the 6-month control regimen of isoniazid, but the rates of tuberculosis in the continuous-isoniazid group markedly increased when therapy was discontinued, which was more common than with the other regimens, probably because of more severe side-effects. These findings are consistent with those of the Botswana trial of continuous isoniazid chemoprophylaxis and suggest ongoing transmission and reinfection in this high-prevalence setting, a phenomenon that is likely to compromise the long-term benefit of any chemoprophylactic regimen, regardless of short-term efficacy.[18] It seems that there is problem of tuberculosis prevention in high-burden settings. There are probably several factors, but the important one is the ongoing transmission and re-infection. Although exogenous re-infection can be assumed to have occurred in patients after continuous isoniazid therapy has been stopped, proving reinfection is difficult, because genotyping of initial and subsequent *M. tuberculosis* isolates is rarely possible. Despite immunization at birth or by early adulthood, most young adults in high-risk settings have been exposed to tuberculosis and infected. Epidemiological considerations suggest that reinfection routinely occurs in these settings, even in HIV-negative populations. Reinfection has been postulated as an essential pathogenic pathway to lung cavitation and pathogen propagation in populations where there is partial immunity from prior vaccination or tuberculosis infection early in life. If this is true, the long-term benefits of chemoprophylaxis are likely to be limited, and if natural infection is not protective, the development of a more effective vaccine will be challenging.[19]

Though India shares 1/5th global burden of tuberculosis with approximately 40% LTBI cases, widespread LTBI treatment is difficult to implement due to limited resources, high rate of false positivity and possibility of development of drug resistance. Moreover, there is not enough evidence for target population screening and treatment.

Since data in developing countries are very limited and unreliable, more trials are needed in India, specially to choose target group for diagnosis, treatment regimens and their success rate with epidemiological impact. Studies are also required to determine the efficacy of the new test in detection of LTBI and prediction of higher risk of developing active tuberculosis.

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The Editor-in-Chief and the members of the Editorial Board of the *Indian Journal of Tuberculosis* wish all its readers a Very Happy and Prosperous New Year 2012.

D. BEHERA
EDITOR

Original Article

IN-HOSPITAL MORTALITY OF INTERMITTENT *VS* DAILY ANTITUBERCULAR REGIMEN IN PATIENTS WITH MENINGEAL TUBERCULOSIS - A RETROSPECTIVE STUDY

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Summary

Introduction: The Revised National Tuberculosis Control Programme (RNTCP), the State-run Tuberculosis Control Initiative of the Government of India, recommends intermittent thrice a week Directly Observed Treatment Short course (DOTS) both during intensive phase and continuation phase for a total of nine months for tubercular meningitis. However, most recent guidelines recommend daily regimen.

***Objective*:** Assessment of the in-hospital mortality in patients with meningeal tuberculosis.

Material and Methods: We retrospectively analyzed the data of patients (n=98) admitted with a diagnosis of meningeal tuberculosis from January 1st 2006 to December 31st 2009 in a tertiary care centre in South India. Thwaites index score of four or less was used for diagnosis of meningeal tuberculosis which is a weighted diagnostic index score for dichotomised clinical variables including age, blood white cell count, duration of illness, CSF total white cell count, and CSF neutrophil percentage. We compared in-hospital treatment outcome of patients on thrice weekly intermittent DOTS regimen with daily regimen patients.

Results: The inhospital mortality was same (27%) in the two treatment regimens (p 0.944). However, there was less incidence of hepatic dysfunction in the intermittent DOTS regimen, even though it was not statistically significant (p 0.148).

Conclusions: In the short term, both regimens have similar mortality outcomes and no statistically significant difference in hepatic dysfunction during the hospital stay. **[*Indian J Tuberc 2012; 59: 6 - 11*]**

Key words: Chronic meningitis, Rifampicin, Treatment outcome, Drug induced liver injury, Steroids.

INTRODUCTION

Central nervous system (CNS) disease caused by *Mycobacterium tuberculosis* is highly devastating, and accounts for approximately 1% of all cases of tuberculosis (TB), of which tuberculous meningitis is the severest form. The diagnostic features of tuberculous meningitis include fever, headache and vomiting altered sensorium or focal neurological deficits, cerebrospinal fluid (CSF) showing pleocytosis, increased protein (> 100 mg/dl) and low sugar (< 60% of corresponding blood sugar)[1]. Prompt diagnosis is crucial for successful disease management; as the case fatality rate for untreated TBM is almost 100% and delay in treatment often leads to permanent neurological damage[2]. The recommended first-line treatment agents for all forms of CNS tuberculosis are Isoniazid(H), Rifampicin (R), Pyrazinamide (Z) and Ethambutol (E) taken daily either individually or in combination form. The standard treatment of TB meningitis has undergone considerable change in the recent past. However, there is no consensus clinical protocol on the anti-tuberculous regimen, and the duration of treatment. The available guidelines vary because the setting, resources, population affected, differ and also due to lack of clinical evidence. The evidences are extrapolated from studies in pulmonary tuberculosis. The duration of treatment also lacks consensus since there is evidence that longer the duration of treatment, less the chance for relapse but at a higher risk of cost, toxicity and poor compliance[3].

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The Revised National Tuberculosis Control programme (RNTCP) is the State-run Tuberculosis Control Initiative of the Government of India. It recommends intermittent thrice a week Directly Observed Treatment Short course (DOTS) both during intensive phase and continuation phase for a total of nine months $\{2(HRZE)_3/7(HR)_3\}$ for tubercular meningitis. The number before the letters refers to the number of months of treatment. The subscript after the letters refers to the number of doses per week. For immunocompromised patients, World Health Organisation (WHO) recommends directly observed daily medication during intensive phase followed by directly observed intermittent therapy thrice a week.

However, most recent guidelines recommend daily regimen for immunocompetent patients also. British Infection Society guidelines recommend daily antituberculous agents for a minimum of 10 months[5]. The American Thoracic Society recommends daily but directly observed treatment during both phases for a total of nine to 12 months[6].

RNTCP in India has completed over eleven years of its implementation. However, it has not been widely accepted for TB affecting the CNS as for pulmonary TB. There are very few reports on intermittent DOTS regimen in meningeal TB[7,8] in adults and hence most doctors continue to give daily antituberculous therapy for variable periods of 12 to 18 months. Venugopal *et al* have reported better compliance with intermittent DOTS regimen among patients with meningeal tuberculosis[7]. With the persistent efforts of RNTCP implementers, there was a slow shift in the use of antituberculous drugs by some of the treating units from daily regimen to thrice weekly intermittent DOTS regimen at our medical facility, from 2006 to 2009. We compared the adverse effects as well as the response to treatment of daily medication with the thrice weekly intermittent DOTS regimen. We tried to look at the inhospital mortality of patients with TB meningitis in view of the scarce data on inhospital outcome in patients on thrice weekly intermittent antitubercular regimen. Our secondary aim was to look at the incidence of hepatic dysfunction.

MATERIAL AND METHODS

Setting

The study design was that of a retrospective review of case records. This retrospective study was undertaken in the Department of Neurology, Government Medical College Hospital, Trivandrum, Kerala, which is a tertiary care referral centre for neurological diseases in South India. From the prospectively maintained database, the case records of all the patients with meningitis from January 1st 2006 up to December 31st 2009 were reviewed.

Subjects

We took patients with a diagnosis of TB meningitis from the case records. These cases were reviewed by one of the authors involved in the study (TI) to determine whether they satisfied the Thwaites index[9]. Different clinical scoring systems have been devised to diagnose meningeal tuberculosis as it is usually paucibacillary and the yield of CSF acid-fast bacillus, culture and polymerase chain reaction (PCR) is very low. In this study, we used the Thwaites index which is obtained by adding up the weighted diagnostic index scores for dichotomised clinical variables. The clinical variables include age, blood white cell count, duration of illness, CSF total white cell count, and CSF neutrophil percentage. We included meningitis patients who met the Thwaites criteria (Thwaites index of four or less) and didn't have another diagnosis (Table 1). Patients with

Table 1: Thwaites diagnostic index scores for clinical variables used for admission and diagnosis of TB meningitis.

Variable	Cut-off	score
Age (years)	≥36	2
	<36	0
Blood WCC (10^3/mL)	≥15 000	4
	<15 000	0
History of illness (days)	≥6	−5
	<6	0
CSF total WCC (10^3/mL)	≥750	3
	<750	0
CSF % neutrophils	≥90	4
	<90	0

WCC=white-cell count; CSF=cerebrospinal fluid.

evidence of bacterial meningitis (Gram stain positivity or culture positivity), cryptococcal meningitis (positive India Ink stain, culture positive or cryptococcal antigen positive), malignant cells in CSF, and evidence of systemic diseases like Weil's disease, leptospirosis and dengue were excluded.

After systematically screening the medical records of all those satisfying the above criteria, we catogorized them into two arms-one group exposed to daily antituberculous treatment and the other managed by intermittent DOTS therapy.

We compared in hospital treatment outcome of patients on intermittent DOTS regimen with daily regimen patients. Both HIV positive as well as negative patients on intermittent DOTS regimen received thrice a week regimen in the intensive as well as continuation phase. We recorded basic demographic data, the co-morbidity, mortality and adverse effects of anti tuberculous therapy (ATT). We staged the patients based on Medical Research Council criteria[10]. Stage 1 patients are fully conscious and have no paresis. Stage 3 are comatose and or have severe paresis. Patients in stage 2 have features in between stage 1 and 3.

Outcome assessment

The response to treatment was judged based on subsidence of fever headache, vomiting and meningeal signs, with concurrent improvement in appetite and weight. Patients were discharged once they showed signs of response. Duration of illness at admission (in days), hospital stay (in days), treatment delay from onset of symptoms (in days), treatment delay from the time of admission (in days), number of days on ATT, hepatic dysfunction (defined as > 3 times elevation in liver enzymes during treatment), in hospital mortality were taken into consideration. We also compared the prevalence of alcohol abuse among the patients on intermittent DOTS regimen and daily regimen. Alcohol abuse was defined as intake of more than two standard drinks per day among males less than 65 years of age.

Statistics

Statistical analysis was done using SPSS 16.0 for windows and GraphPad Prism 5. Continuous variables were analysed by independent Student's t test and categorical variables were analysed by Chi square test and Fisher's exact test. Statistical significance was indicated by a p value < 0.05.

RESULTS

Clinical characteristics

A total of 98 cases (55 in the intermittent DOTS arm and 43 in the daily regimen arm) were studied out of a total of 122 cases. Twenty four cases were rejected as per the exclusion criteria. The 55 patients on intermittent DOTS regimen had a mean age of 37 years, of which 21 were females (38%) and 22(40%) had a contact with TB. 43 patients on daily regimen had a mean age of 39.4 years, of which 18 were females (42%) and 18(42%) had a contact with TB. The two groups did not differ in the baseline characteristics like demography, extraneural involvement, comorbidity, clinical features, severity and steroid use (Table 2).

Laboratory parameters

There was no hyponatraemia in 21 patients (38.2%) on the intermittent DOTS regimen compared to 11 patients (25.6%) on daily regimen. The mean albumin level was 3.442 gm/dl in patients on the intermittent DOTS regimen compared to 3.260 gm/dl in patients on daily regimen. CSF Glucose was d"30mg/dl in 22(40%) in the intermittent DOTS regimen while it was 15(34.9%) on daily regimen. CSF Protein >100mg/dl was seen in 14(25.5%) in the intermittent DOTS regimen while it was 10(23.3%) on daily regimen. None of these parameters tested attained statistical significance.

Response to treatment and outcome

The inhospital mortality was same (27%) in the two treatment regimens (p=0.944). Fifteen patients out of the 55 patients on the intermittent DOTS regimen and 12 out of 43 patients in the daily regimen died (Table 3). The commonest cause of death in both intermittent DOTS regimen (three patients) and daily regimen (six patients) was raised intracranial pressure.

Table 2: Comparison of patient parameters on intermittent DOTS and daily anti-tubercular regimens

		Intermittent DOTS n (%)	Daily regimen n(%)	p value
Number of patients		55	43	0.351
Demography	Mean age (years)	37.07	39.47	0.387
	Female sex	21(38.2%)	18(41.9%)	0.71
	Alcohol abuse	8(14.5%)	13(30.2%)	0.06
	Smoking	10(18.2%)	10(23.3%)	0.536
	Contact with PT	22(40%)	18(41.9%)	0.851
Extraneural TB	Pulmonary	16(29.1%)	13(30.2%)	0.903
	Sputum AFB	2(3.6%)	1(2.3%)	0.709
Co morbidity	HIV positive	7(12.7%)	3(7%)	0.351
	Abnormal USS abdomen	12(21.8%)	5(11.6%)	0.371
	Coexistant tuberculoma	5/44(11.36%)	2/40(5%)	0.257
Clinical features	Seizures	14(25.5%)	17(39.5%)	0.137
	No Hemiplegia /paresis	36(65.5%)	28(65.1%)	0.373
	Aphasia	13(23.6%)	6(14%)	0.199
	Hydrocephalus	20/44(45.45%)	18/40(45%)	0.938
	Papilledema	16(29.1%)	15(34.9%)	0.541
	Optic atrophy	0	0	
	Bulbar paralysis	1(1.82%)	0	
Severity	MRC stage 1	24(43.6%)	11 (25.6%)	
	MRC stage 2	25(45.5%)	30(69.8%)	0.053
	MRC stage 3	6 (10.9%	2(4.7%)	
	Glasgow Coma Scale	14.22	13.30	0.098

USS=ultrasound scan, HIV=human immunodefeciency virus, MRC-medical research council.

Table 3: Comparison of treatment outcomes of patients on intermittent DOTS and daily anti-tubercular regimens

		Intermittent DOTS Median (IQR) / n (%)	Daily regimen Median(IQR) / n (%)	p value
Treatment	Duration of illness at admission (days)	15 (23)	14 (14)	**0.2145**
	Hospital stay (days)	11 (11)	13 (11)	**0.8945**
	Treatment delay from onset of symptoms (days)	21 (17)	18 (14)	**0.2164**
	Treatment delay from the time of admission (days)	5 (5)	3 (3)	**0.2001**
	Steroid	42(76.4%)	33(76.7%)	0.933
Outcome	Hepatic dysfunction during treatment	3(5.46%)	6(13.95%)	0.148
	In-hospital mortality	15 (27.3%)	12(27.9%)	0.944

IQR - Interquartile range

The other causes being sepsis (three patients in intermittent DOTS and one in daily regimen), aspiration pneumonia (two patients in intermittent DOTS and one in daily regimen), and disseminated TB (two patients in intermittent DOTS and one in daily regimen), Immune reconstitution inflammatory syndrome was the cause of death in one patient in the intermittent DOTS regimen while one patient in the daily regimen died of arteritis. Cause of death in six patients (four in intermittent DOTS regimen and two in daily regimen) could not be determined.

The rate of hepatic dysfunction during this period in the intermittent DOTS regimen 3(5.46%) differed from that of daily regimen 6(13.95%) but did not attain statistical significance (Table 3). None of the patients with hepatic dysfunction were on other hepatotoxic drugs or were taking alcohol while on ATT. Viral hepatitis was excluded using viral markers. There were no other adverse drug reactions.

DISCUSSION

This is the first study comparing the in-hospital mortality between DOTS *Vs* daily antitubercular regimen in patients with meningeal tuberculosis. We found no statistically significant difference between in-hospital mortality in daily regimen and intermittent DOTS regimen. The overall in-hospital mortality in our study (27%) was comparable to the existing literature (14.3% to 69.6%)[11-14]. In the study by Karstaedt *et al* on culture-proven TBM in South African urban adults, the mortality rate was 69 % which was higher compared to current study but they had 72% patients with human immunodeficiency virus (HIV) infection compared to only 10% in our study[15].

A high proportion of our patients (40.82%) had a history of contact with pulmonary tuberculosis, which is consistent with literature on adult patients[16,17]. **Therefore, history of contact should always be sought in all patients presenting with subacute and chronic meningitis**. The incidence of hepatic dysfunction during hospitalization was 9.18% in our study. The rate of hepatic dysfunction was more in the daily regimen (not statistically significant) which may be due to the higher proportion of patients taking alcohol in the daily regimen(not statistically significant) (Table 1).

The major limitation is the retrospective nature of the study. The numbers were small and the study was under powered to show the real difference. The number of patients abusing alcohol in the daily regimen was more even though statistically not significant. The comparison between the two regimens was done only for the period of initial hospitalization and follow up was unavailable which was needed to compare the long term morbidity, mortality and recurrence rate after stopping treatment. However, there are no studies comparing daily regimen with intermittent DOTS regimen of antituberculous treatment in meningeal tuberculosis to the best of our knowledge. This study was an attempt to compare intermittent DOTS regimen and daily regimen with all the limitations of a retrospective study.

There is a need for larger multicentric prospective randomised controlled studies of patients with meningeal tuberculosis on intermittent DOTS regimen to look at the mortality and morbidity. Only such data will help to decide on the adequacy of the current regimen as well as on the duration of treatment.

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Original Article

IMPACT OF THE RNTCP IRL-EQA-OSE VISITS ON QUALITY OF SPUTUM SMEAR MICROSCOPY SERVICES OF GUJARAT, INDIA

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Summary

Objective: On-site evaluation of laboratories with standard checklist is a first step to promote effective and consistent supervision. The present study was carried out to evaluate the impact of the RNTCP- Intermediate Reference Laboratory External Quality Assessment- On-Site Evaluation visits on quality of sputum smear microscopy services of Gujarat, India. Data of three IRL-EQA-OSE visit rounds, carried out between January 2005 and December 2010 are presented here.

Material and Methods: Within the Revised National Tuberculosis Control Programme EQA framework, the IRL, Ahmedabad visited all Gujarat District Tuberculosis Centres, and evaluated their sputum smear microscopy services. The study covered a cohort of 29 DTCs during each of the three IRL-EQA-OSE visits. The authors focused on section III of Annexure A to study and analyse the said impact. In order to convert qualitative data into quantitative one, the authors denoted a score of 1 to "Acceptable" (No Error) remark and 0 to "Not-Acceptable" (Error) one.

Results: A larger degree of improvement was noted in Standard Operating Procedure practices, Disinfection practices, and Internal Quality Control practices. Many DTCs did not retrain their laboratory staff in EQA methodology. The Gujarat DTCs achieved an overall score of (820/957) 86% during the initial OSE visits which consistently improved to (842/957) 88% and (885/957) 92% during the two follow-up OSE visits along with sustenance and improvement in many important laboratory parameters.

Conclusion: The co-sponsoring organisation (IRL) recognises the challenges and therefore, is committed to supporting state-level implementation of EQA through additional training, technical assistance to districts, and improving this technical guidance. By periodic IRL-EQA-OSE visits, sputum smear microscopy services can be sustained and improved at field level. **[*Indian J Tuberc 2012; 59:* 12 - 17]**

Key words: IRL, EQA, OSE, Laboratory Services, QI, RNTCP

INTRODUCTION

Effective control of tuberculosis (TB) is dependent on a network of local laboratories that provide accurate and reliable direct acid fast bacilli (AFB) microscopy testing for diagnosis, treatment, and monitoring. The availability and quality of AFB microscopy relies on national programmes that support, train, and monitor the testing performance of individual laboratories. Quality Assurance (QA) is a total system consisting of internal Quality Control (QC), assessment of performance using External Quality Assessment (EQA) methods, and continuous Quality Improvement (QI) of laboratory services. EQA should be implemented in areas or regions where the DOTS is well established. On-Site Evaluation (OSE) includes regular visits by the district superviser under the National or Regional TB Programme, as well as an annual visit by a laboratory supervisor from a higher-level laboratory. External Quality Assessment is one component of a laboratory QA programme.[1]

To optimise QA, decentralisation of the supervision and monitoring of the laboratory network is essential, and capacity building of the states to undertake these activities becomes a priority. This

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process requires the active support and participation of the respective administrative levels in the country. The higher level laboratories (National Reference Laboratories [NRLs]/ Intermediate Reference Laboratories [IRLs]) must have the capacity to plan and implement quality assurance activities in a well-organised fashion. They should be capable of ensuring action that leads to improved quality and performance of the Designated Microscopy Centre network. The Revised National Tuberculosis Control Programme (the RNTCP, India) has established a system to monitor laboratory practices based on the International Union Against Tuberculosis and Lung Disease and World Health Organisation guidelines. The NRLs provide training to all IRL personnel who are responsible for on-site evaluation. Additionally, non-laboratory personnel (e.g., District Tuberculosis Officers) should acquire working knowledge of routine laboratory operations, including proper RNTCP procedures, appropriate supplies, laboratory safety, basic microscope operations, and requirements of panel testing or rechecking programmes operated by the RNTCP. Laboratory supervisers must be knowledgeable in all operational and technical elements of AFB smear microscopy, and have sufficient expertise to observe technicians performing routine tasks. They should also facilitate quality improvement through on the spot problem solving and suggestions for corrective action wherever needed.[2]

The focus of EQA is on the identification of laboratories where there may be serious problems resulting in poor performance, not on the identification of individual slide errors or the validation of individual patient diagnoses. On-site evaluation of laboratories with standard checklist is a first step to promote effective and consistent supervision.[1]

The Intermediate Reference Laboratory, Ahmedabad is conducting External Quality Assessment-On-Site Evaluation visits of all Gujarat DTCs since January 2005. Despite EQA being an integral part of the Revised National Tuberculosis Control Programme (the RNTCP, India) since 2005, not much of the scientific data analysis is forthcoming on this subject. The present study was carried out to evaluate the impact of the RNTCP Intermediate Reference Laboratory- External Quality Assessment- On-Site Evaluation visits on sputum smear microscopy services of Gujarat, India. We present data of three such visit rounds, carried out between January 2005 and December 2010.

MATERIAL AND METHODS

Gujarat had implemented EQA programme at the highest level since its inception in 2005. Within the Revised National Tuberculosis Control Programme EQA framework, the IRL, Ahmedabad visited all Gujarat District Tuberculosis Centres (DTCs), and evaluated their sputum smear microscopy services. The study covered a cohort of 29 DTCs during each of the three IRL-EQA-OSE visits. The IRL team headed by IRL Microbiologist/ Bacteriologist/ Director visited each of the above mentioned DTCs for two to three days. The standard Annexure A for IRL-EQA-OSE[2] was consistently used for evaluation purpose during all the OSE visit rounds (Table). This comprehensive checklist yields data that can easily be entered into a database for long-term tracking and comparing performance. Section III of Annexure A deals with total 33 defined laboratory items which are divided into- infrastructure, standard operating procedure (SOP), adequate stock and supply of laboratory consumables, staining reagents/ equipment, binocular microscope, disposal of infected materials, safety practices, training status, internal quality control, and external quality control- parameters of particular DTC.

The IRL team performed on-site evaluation of DTCs and examined above said parameters. Good laboratory practices along with practical problems were listed out in Annexure A. The District Tuberculosis Officers (DTOs) were given on-site suggestions. A detailed IRL-EQA-OSE report suggesting possible source of errors and remedial actions was submitted to the DTOs. The DTOs implemented respective corrective actions based on IRL-EQA-OSE report.

The authors focused on section III of Annexure A to study and analyse the impact of IRL-EQA-OSE visits. In order to convert qualitative data in to quantitative one, the authors denoted a score of 1 to "Acceptable" (No Error) remark and 0 to "Not-Acceptable" (Error) one. This scoring system could have yielded the highest possible score of 33 for each DTC per OSE visit, and 957 for all Gujarat DTCs during the initial visits and two follow-up OSE visit rounds.

Table: Annexure A- III Current visit particulars[2]

Sl. No.	Item	Adequate/ Acceptable	Problems Identified
1	Infrastructure: Separate area for EQA Lab work Separate tables for re-staining and smear microscopy for RBRC		
2	Power supply		
3	Running water supply		
4	STLS: Training in RNTCP/ EQA		
5	LT: Number and training in RNTCP/ EQA		
6	Standard Operating Procedure: Follow smear preparation and staining procedure		
7	Follow grading chart		
8	Follow EQA Protocol		
9	Adequate stock and supply of: Slides		
10	Lens tissue		
11	Filter paper		
12	Spirit lamp or bunsen burner		
13	Immersion oil		
14	Disinfectants (5% PHENOL)		
15	Smearing/staining equipment (staining racks, loops, sticks etc)		
16	Slide boxes		
17	EQA forms		
18	Staining reagents / equipment:		
19	1% Carbol fuchsin		
20	0.1% Methylene Blue		
21	25% Sulphuric acid		
22	Distilled water		
23	Equipment for preparation of stains / reagents such as balance (for weighing reagents) and measuring cylinder etc		
24	Binocular microscopes		
25	Disposal of infected material: Waste containers with lid		
26	Waste disposal by Autoclave / disinfection / buried		
27	General order/cleanliness		
28	Safety Practices		
29	Training status: Any change in staff since last supervisory visit.		
30	Has each STLS undergone training/ refresher training in EQA within past two years		
31	Internal Quality Control: Are all STLS using positive and negative control slides for internal quality control of each new batch of stain as required by the RNTCP?		
32	External quality control: All DMCs are visited at least once in a month by STLS during the current period of the year		
33	Are all slides kept as required by the RNTCP EQA Programme?		

RESULTS

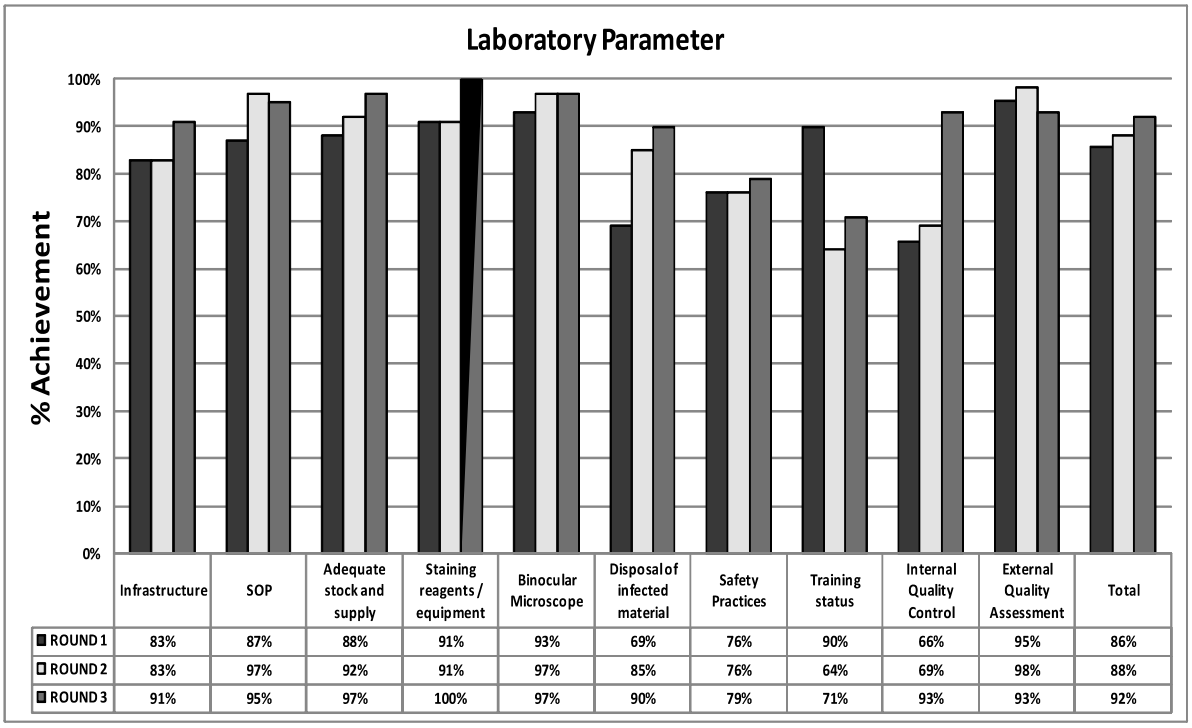
All DTCs scored 100% in "Power supply", "Adequate stock and supply of: Slides", "Adequate stock and supply of: Lens tissue", and "Adequate stock and supply of: Spirit lamp or bunsen burner" during the entire evaluation phase.

Initially, 5% phenol for disinfection purpose was used by (9/29) 31% DTCs which parameter improved to (23/29) 79% DTCs during the second OSE round, and touched (29/29) 100% in the final round.

Similar improvement was documented in infrastructure parameter with (132/145) 91% in the third OSE visit against (121/145) 83% during the first and the second OSE visits. The SOP parameter corrected at (84/87) 97% and sustained at (83/87) 95% during the second and the third OSE visits respectively, against the baseline score of (76/87) 86% during the first OSE visit. Staining reagents/ equipment parameter got bettered from (158/174) 91% during the first and the second OSE visits to (174/174) 100% in the third OSE visit. Disposal of infected material at DTCs steadily improved form (60/87) 69% to (74/87) 85%, and reached (78/87) 90% on a sequential basis. Internal Quality Assessment parameter also witnessed consistent positive growth starting from (19/29) 66% in the first OSE visit to (20/29) 69% in the second OSE visit, and finally attained (27/29) 93% in the third OSE round.

While sustenance was observed in Binocular Microscope (27/29; [93%], 28/29; [97%], 28/29; [97%]), Safety practices (22/29; [76%], 22/29; [76%], 23/29; [79%]), and External Quality Assessment (55/58; [95%], 57/58; [98%], 54/58; [93%]), a huge drop in Training status from (52/58) 90% in the first OSE round to (37/58) 64% in the second OSE round was documented, which jumped to (41/58) 71% in the final OSE round.

The Gujarat DTCs achieved an overall score of (820/957) 86% during the initial OSE visit which steadily improved to (842/957) 88% during the second OSE visit, and to (885/957) 92% during the third OSE visit, along with sustenance and improvement in many important laboratory parameters (Chart).



	Infrastructure	SOP	Adequate stock and supply	Staining reagents / equipment	Binocular Microscope	Disposal of infected material	Safety Practices	Training status	Internal Quality Control	External Quality Assessment	Total
ROUND 1	83%	87%	88%	91%	93%	69%	76%	90%	66%	95%	86%
ROUND 2	83%	97%	92%	91%	97%	85%	76%	64%	69%	98%	88%
ROUND 3	91%	95%	97%	100%	97%	90%	79%	71%	93%	93%	92%

Chart: Percentage score achievement in section III of Annexure A during OSE visits

DISCUSSION

Quality Assurance of laboratory services is a complex issue highly dependent on resources in the country or region, structure of the health system and laboratory network, and incidence of disease. On-Site Evaluation visits to the peripheral laboratories by trained laboratory personnel from the reference or intermediate laboratory are essential if performance is to be improved or maintained at a high standard. These visits allow for the observation of worker performance under actual conditions, including condition of equipment, laboratory safety, adequacy of supplies, and the process for smearing, staining, reading, recording and reporting. Direct contact between the supervisor and the technicians motivates staff to improve performance.[1] The significance of OSE has been repeatedly documented.[3-5] Gujarat state's efforts in IRL-EQA-OSE visits had been acclaimed by respective supra-national reference laboratory (Tuberculosis Research Centre, Chennai).[5]

In order to develop and implement EQA, a separate fully functional microscopy centre, trained laboratory staff, quality power supply, running tap water, etc., should be available in the DTC.[1] Gujarat state had implemented sputum smear microscopy services as per international standards since long. While *some* IRLs faced problems with *items* like "well-equipped laboratories", "adequate stocks of consumables" and "trained staff",[5] Gujarat DTCs did not find fulfillment of these parameters problematic for their sputum smear microscopy services. It is noteworthy that all DTCs scored 100% in "Power supply", "Adequate stock and supply of: Slides", "Adequate stock and supply of: Lens tissue", and "Adequate stock and supply of: Spirit lamp or bunsen burner" during the evaluation phase.

The first priority in infection control is the use of administrative control measures to prevent the generation of infectious droplet nuclei, thereby reducing the exposure of the health care workers (HCW) and patients to *Mycobacterium tuberculosis* bacilli. Measures include patient education, correct sputum collection, achievement of early detection and high cure rate among smear positive pulmonary tuberculosis patients, strict adherence to laboratory SOPs, and adequate training of HCWs to implement the infection control plan. Proper waste disposal with 5% phenol is recommended in the RNTCP.[2] The temporal killing action of disinfectants depends on the population of organisms to be killed, the concentration used, the duration of contact and the presence of organic debris.[6] The important laboratory parameters like SOP practices and bio-medical waste management practices witnessed a larger degree of positive impact by the OSE visits.

All HCWs working at the district level should receive ongoing education at least once a year regarding the basic concepts of *M. tuberculosis* transmission and pathogenesis, the signs and symptoms of TB, the increased risk of TB disease in persons with HIV infection, and other immunosuppressive conditions, who also are infected with *M. tuberculosis.*[2] Such measures might prove helpful to successfully implement safety measures among HCWs.

We found that district laboratory supervisers did not practise internal quality control practices initially (19/29; [66%]), however they did improve to a satisfactory level during subsequent visits with a tardy pace (20/29; [69%], 27/29; [93%]). However, this finding is against stark contrast of consistently achieving more than 90% in external quality assessment parameter during the study period. Implementing EQA will require each DTO to devote time and direct his staff to understand some complex technical and logistical issues and then select the methods that are most appropriate for the district.

Binocular microscopes are required for detecting acid fast bacilli in sputum smear and other material for use in the RNTCP laboratories, including those at peripheral health centres.[2] The IRL supervisors should ensure that at least one functional binocular microscope is available in the DTC. We found that (27/29) 93% DTCs had at least one functional binocular microscope during the first OSE visit round which rose to (28/29) 97% during the subsequent OSE visits. The state had provided an exclusive binocular microscope to all DTCs for district EQA programme facilitation. In addition, the state had entered into an annual maintenance contract of all binocular

microscopes to keep them in sound working order as well.

Quality improvement is a process by which the components of smear microscopy diagnostic services are analysed with the aim of looking for ways to permanently remove obstacles to success. Data collection, data analysis, and creative problem solving are the key components of this process. It involves continued monitoring, identifying defects, followed by remedial action including re-training when needed, to prevent recurrence of problems. Quality improvement often relies on effective on-site evaluation visits. Owing to many variables that can affect laboratory performance, and the potential for these factors to change over time, it is recommended that rechecking be continued even after consistently good performance is achieved.[1] A dramatic fluctuation in training status parameter of laboratory personnel, in chronological order from (52/58) 90% to (37/58) 63% and (41/58) 71% could be one example of its own kind.

CONCLUSION

The co-sponsoring organisation (IRL) recognises the challenges and therefore, is committed to supporting state-level implementation of EQA through additional training, technical assistance to districts, and improving this technical guidance. By periodic IRL- EQA-OSE visits, sputum smear microscopy services can be sustained and improved at field level.

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Original Article

AN EPIDEMIOLOGICAL STUDY OF MULTI DRUG RESISTANT TUBERCULOSIS CASES REGISTERED UNDER REVISED NATIONAL TUBERCULOSIS CONTROL PROGRAMME OF AHMEDABAD CITY

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Summary

***Background*:** The emergence of resistance to anti-tuberculosis drugs in general and Multi Drug Resistan Tuberculosis (MDR-TB) in particular, has become a significant public health problem and an obstacle to effective TB control. Baseline and adequate information on epidemiological factors and their interaction are prerequisites for its effective control.

***Objectives*:** To study socio-demographic profile, housing environment, health-seeking behaviour, present and past history regarding treatment of tuberculosis, drug resistance pattern and the preventive practice adopted by the patients.

***Methodology*:** A cross-sectional study was carried out on 81 MDR-TB patients registered under RNTCP of Ahmedabad city during July 2007-June 2008. To accomplish the objectives, information was collected by personal interviews using pre-designed, pre-tested proforma. Data, so collected, was analyzed and tabulated using appropriate statistical software.

***Results*:** More than 2/3rd were males and majority were in age group 16-45 years, educated up to primary level, living in overcrowded and ill-ventilated houses. Initially almost all had pulmonary TB. At the start of category II, maximum number of patients were defaulters, the prime cause being financial crunch. The mean number of Anti Tubercular Treatment (ATT) taken before start of category IV was 2.85. More than 90% experienced side-effects of drugs. Although indiscriminate spitting was less, other methods of sputum disposal were also unsafe. Resistance to all four drugs (H, R, S & E) was found in more than 2/3rd of cases. Smear and culture conversion rate at three month follow up was 62.0% and 58.7% respectively. Only one patient (1.2%) was reactive for HIV in the study. Most of the patients perceived some degree of improvement in their condition following treatment.

***Conclusion*:** Most of the MDR cases were living in poor envirmental conditions, had previous history of TB and defaulter of treatment regimen prescribed. Motivation of private practitioners for increasing referrals, use of incentives and enablers, enhancing contact tracing and increasing awareness regarding sputum disposal practices and measures to prevent the spread are necessary for effective control of tuberculosis. **[*Indian J Tuberc 2012; 59: 18 - 27*]**

***Key words*:** Multi drug resistant, Tuberculosis, Epidemiology.

INTRODUCTION

Tuberculosis (TB) is a major cause of illness and death worldwide, especially Asia and Africa[1]. There are 22 high burden countries which account for 80% of all estimated incident cases worldwide. Among such countries, India ranks first with two million estimated TB cases as against estimated global annual incidence of 9.4 million accounting for 21% of world's new TB cases[2].

The emergence of resistance to anti-tuberculosis drugs in general and MDR-TB, in particular, has become a public health problem of prime concern in a number of countries and a major bottleneck in effective TB control.[3] As per the estimation of WHO, there are nearly half a million MDR-TB hit new cases every year, which is about 5% of nine million new TB cases of all types[3]. Management of MDR-TB is a challenge which requires prolonged use of expensive second-line drugs with a significant potential for toxicity[4]. Mismanagement of MDR-TB may lead to development of the Extensively Drug-Resistant Tuberculosis (XDR-TB), a virtually untreatable form of TB, which has been recorded in 45 countries[3,5]. Patients with XDR-TB would have to be managed like TB patients in pre-antibiotic era. The economic, social and health security of countries and communities with a high prevalence of TB would be threatened by virtually untreatable TB among the bread-

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winners, parents and economically productive age groups[6].

In India, prevalence of MDR-TB is found to be 2.8% in new cases and 17.2 % in previously treated cases[7]. For the appropriate management of MDR-TB patients, Revised National Tuberculosis Control Programme (RNTCP) has initiated DOTS- Plus activities from August, 2007 in Ahmedabad, a premier city of Gujarat State[2]. RNTCP has developed national guidelines[8] based on the WHO recommended international DOTS-Plus guidelines[2].

The disease is not only a medical problem or a public health problem but is also a critical social problem of great magnitude[9]. Baseline and adequate information on epidemiological, social, economic and cultural factors and their interaction is required for its control and effective treatment[10].

With this background, the present study was conducted among MDR-TB patients registered for DOTS Plus therapy under RNTCP of Ahmedabad city with a view to get the information regarding socio-demographic profile, housing environment, health-seeking behaviour, present and past history regarding treatment of tuberculosis, social and other problems faced during treatment, drug resistance pattern and the preventive practice adopted by the patients for preventing its spread.

METHODOLOGY

Study setting

The present study was conducted in Ahmedabad, a premier city of Gujarat State in western part of India. The city is divided into six Municipal zones and there are 10 Tuberculosis Units (TUs) in the city. It was a cross-sectional descriptive study carried out during August 2007 to October 2009.

Study population

Study Population consisted of MDR-TB cases registered under DOTS Plus of RNTCP of the city from third quarter 2007 to second quarter, 2008 excluding those patients who died or migrated before the home visit by the interviewers. Total 92 patients were registered under DOTS Plus register, of which 11 patients were excluded. Therefore, 81 patients were included for complete analysis. However, a few of socio-demographic information i.e. age and sex and results of sputum smear and culture could be obtained of all 92 cases from the DOTS Plus register.

Study method

A list of MDR-TB patients registered during the study quarters under DOTS Plus was obtained from State TB Training and Demonstration Centre (STDC) after obtaining permission from the concerned authority. With the help of Senior Treatment Supervisors (STS) and TB Health Visitors (TBHVs) of each of the 10 TUs, home visits of all the patients were carried out after completion of at least 10 months treatment, average being 15 months. All information to accomplish objectives was collected by personal interview of each of the study subjects for 30 to 45 minutes at the time of home visit by one of the investigators using pre-designed and pre-tested proforma. The proforma contained structured questionnaire comprising questions for socio-demographic profile, housing environment, health-seeking behaviour, present history including symptoms, treatment and its side effects, problems faced during treatment, past history regarding treatment of tuberculosis, contact history, drug resistance pattern and the preventive practice adopted by the patients. Subjective perception of improvement in the condition of the patients undergoing DOTS Plus treatment, excluding defaulters, was assessed by asking percentage improvement in their condition. General impression regarding DOTS Plus was also assessed, by inquiring about the difficulties faced by them in approaching health care provider at DOTS Plus site or other health facility, behaviour of DOT provider or other health personnel and about their overall feeling about the efficacy or otherwise of the treatment. The

results for HIV reactivity, sputum smear and culture and drug susceptibility testing (DST) were obtained from the records of the patients available at respective TUs. At the RNTCP accredited laboratory, solid egg-based Lowenstein-Jensen (LJ) media was used for culture and DST was performed for Streptomycin (S), Isoniazid (H), Rifampicin (R) and Ethambutol (E) using economic variant of proportion method on LJ media as per the national guidelines.

Definitions used in study

- MDR-TB Suspect: A Category II patient who is smear positive at the end of the fourth month of treatment or later[8].
- Literate: Person who can read and write with understanding in any one language.
- Overcrowding: Said to be present if floor space area per person is less than 50 square feet.
- Ill ventilation: Said to be present if door and window area combined is less than 2/5th of floor space area.
- Contact/ contact person: The person with confirmed pulmonary TB disease with whom patient might have shared the air environment. Exposure may be close or casual.
- Treatment outcome of contact person: Treatment outcome of a TB case with whom patient might have shared the air environment.
- Secondary case: Person developing the disease following contact to index case.
- Addict: Includes tobacco chewer, smokers or alcohol takers who are regularly taking the same for $\geq$ 6 months.
- Ex addict: Includes Ex-tobacco chewers, Ex-smokers or Ex-alcohol takers; those who had formerly smoked or taken alcohol regularly for $\geq$ 6 months but got rid of the habit for $\geq$1 year since the time of interview.

Data analysis

Data so collected was then analyzed and tabulated using Microsoft Excel and SPSS 11.5. Analysis was done by finding out means and proportions and by applying tests of significance i.e. z test, standard error of difference between two proportions and chi-square test.

RESULTS

Socio demographic profile (Table 1)

Age and Sex details were available for all 92 patients while other details were available for 81 patients. In the study population, 83.7% of patients were in the reproductive age group of 16-45 years with mean age of 33.64 + 11.03 years. Sixty three (68.5%) were males and 29 (31.5%) were females. Literacy rate was 86.4%, of which 61.4% had primary education. Majority of the patients belonged to Hindu religion (70, 76.1%) followed by Muslim and Christian. There were 53 (65.4%) patients belonging to nuclear family and rest to the joint family. Most of the patients 55 (67.9%) were married. Majority of patients belonged to the upper lower class (class IV) of Modified Prasad's[11] and Kuppuswamy's[12] Classification. At the time of interview, 45 (55.6%) patients were either unemployed or occasionally going for work. While before start of Category IV, only 13 (16.0%) such patients, which indicates that around 40% of the patients became incapacitated for work after starting Category IV treatment and the difference is statistically significant. ($z= 5.77$, $p< 0.01$)

Housing environment

Overcrowding in the house was found in 47 (58.0%) patients. In the houses of 70 (86.4%) patients, ventilation was inadequate.

Health-seeking behaviour and habits

For minor illnesses, about 80% were visiting the private practitioners while rests were attending either Municipal hospitals or Government hospital. However, for major illnesses, most patients gave their preference for municipal hospitals. Scar of BCG vaccine was absent in more than 80% of patients. There were 35 (43.2%) patients who never had tobacco or alcohol, 26 (32.1%) patients were ex-addicts and 20 (24.7%) patients were addicted at the time of interview.

Table 1: Socio Demographic Profile of Study Subjects

Sr. No.	Demographic Variable	No. of Patients	Percentage
1	**Age (n=92)**		
	16-25	28	30.4%
	26-35	25	27.2%
	36-45	24	26.1%
	46-55	14	15.2%
	56-65	1	1.1%
2	**Sex (n=92)**		
	Male	63	68.5%
	Female	29	31.5%
3	**Education (n=81)**		
	Illiterate	12	14.8%
	Primary (Std. 1-7)	43	53.1%
	Secondary (Std. 8-10)	21	25.9%
	Higher Secondary (Std. 11-12)	2	2.5%
	Graduate	3	3.7%
4	**Religion (n=92)**		
	Hindu	70	76.1%
	Muslim	21	22.8%
	Christian	1	1.1%
5	**Type of Family (n=81)**		
	Nuclear	53	65.4%
	Joint	28	34.6%
6	**Marital Status (n=81)**		
	Married	55	67.9%
	Unmarried	19	23.5%
	Widow/er	4	4.9%
	Separated / Divorced	3	3.7%
7	**Present Employment status (n=81)**		
	Employed	36	44.4%
	Unemployed/ occasionally going for work	45	55.6%
	Past Employment status (n=81)		
	Employed	68	84.0%
	Unemployed/ occasionally going for work	13	16.0%

In the present addicts, in 85%, type of addiction was of tobacco in any form, of which tobacco chewing was the most common. In ex-addicts also, the most common type of addiction was of tobacco, of which smoking was the most common.

Presence of BCG Scar

Scar of BCG vaccine was absent in more than 80% of patients.

History of study subjects as regards contact with TB case/s

Thirty nine (48.2%) patients gave history of contact with a confirmed case of TB before they themselves got affected by TB. Average number of cases to whom the study subjects were exposed was 1.43 per patient. In about 85%, such case was a family member followed by neighbour, colleague at workplace and from occupation (DOT provider). When treatment outcome of such cases was asked, in 23 (59%) patients, the outcome was death followed by cure in 10 (25.6%) patients, not known in five (12.8%) patients and still on treatment in one (2.6%) patient.

Past and present history of TB

Forty three (53.1%) patients visited at least one doctor/health care provider before coming to RNTCP. Forty nine (60.5%) patients started ATT from RNTCP while 32 (39.5%) started from private health facility. In 63% patients, referral to RNTCP was by Government/ Corporation Doctor. Only 12% of referrals were by private practitioners.

At the beginning, almost all patients, 80 (98.8%) had pulmonary tuberculosis and only 1 (1.2%) patient had extra-pulmonary tuberculosis. At the start of category II, the reason was default in 25 (30.9%) patients followed by relapse in 23 (28.4%) patients, failure in 22 (27.2%) patients and others in 11 (13.5%) patients. The most common reason for default was financial problem, (in 48.0%) followed by no improvement in symptoms (in 32.0%). Other reasons for defaulting were side-effects of drugs, migration, alcohol and improvement in condition.

There were nine (10.8%) patients who used other systems of medicine at any point of time during TB treatment.

Mean number of ATT and regularity of treatment

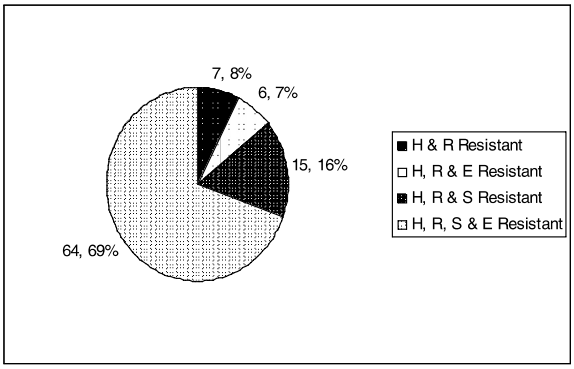
The mean number of ATT taken before start of category IV was 2.85. Most patients (87.7%) were regular during their last ATT. The reasons for irregularity found were side-effects, migration, alcohol, riots, patient's non-cooperation and type of occupation. Female sex was found to be significantly regular during last ATT. However, no significant difference was found between education of the patient and regularity of treatment.

Symptoms

Regarding symptoms at start of category IV treatment, cough with expectoration (79, 97.5%) was the most common. Other symptoms were fever (95.1%), anorexia and weight loss (91.4%), breathlessness (38.3%), hemoptysis (23.5%), chest pain (22.2%), weakness (9.9%) and abdominal pain (1.2%). Six (7.4%) patients had co-morbidity with TB, of whom five had Diabetes Mellitus while one patient was suffering from valvular heart disease.

Resistance pattern and HIV

DST results showed that in about 70% of the patients, resistance to all four drugs (H, R, S and E) was present followed by H, R and S (16.3%) resistance; H, R and E (6.5%) resistance and H and R resistance (7.6%) (Fig. 1). Only one (1.2%) patient was found HIV positive.



H- Isoniazid, R- Rifampicin, S- Streptomycin, E- Ethambutol

Figure 1: Result of drug sensitivity testing

Status of patient in Category IV

At the time of interview, 75 (92.6%) patients were on treatment while six (7.4%) patients were defaulters, of whom in five (83.3%), the reason was side effects and non-cooperation in one (16.7%) patient.

Adverse drug reactions

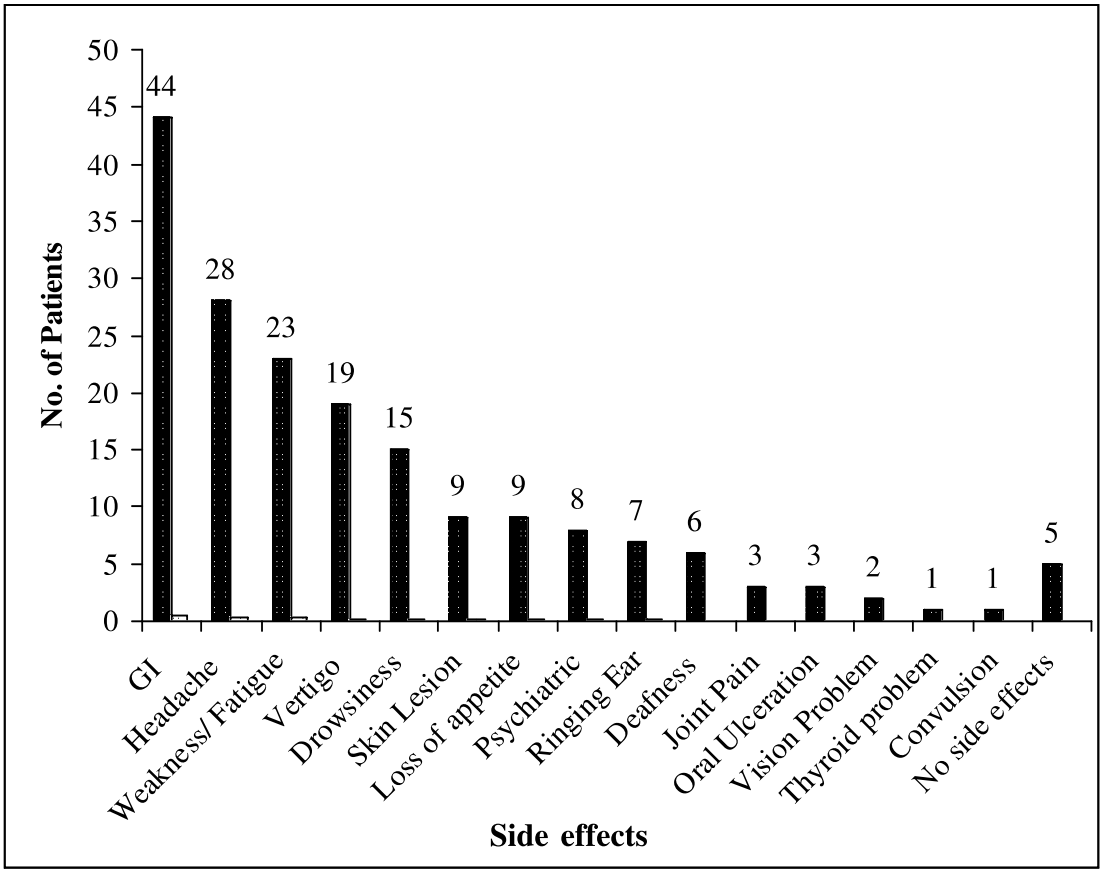
Seventy six (93.8%) patients experienced one or the other side effect of drugs. Gastro intestinal symptoms were the most common. However, serious side effects like psychiatric problems, ringing in ear, deafness, thyroid enlargement and convulsion though in lower proportion were also seen. (Fig. 2)

Problems during treatment

Most patients faced problems during initial months of treatment. Most of them, 39 (48.1%) had loss of wages followed by inability to do household work in 26 (32.1%) patients. However, 18 (22.2%) patients didn't face any social problem so far.

Culture conversion

The trend of sputum culture result during follow up period up to 12 months was studied. The culture conversion rate in available results was 62.8%, 62.2%, 67.5%, 67.2%, 65.7%, 64% and 81.5% at 3rd, 4th, 5th, 6th, 7th, 9th and 12th month of follow up respectively. No significant (p> 0.05)



* More than one side effect was present per patient.

Figure 2: Side effects experienced by patients

gender difference was found. (Table 2 and Fig. 3)

Perception of improvement following DOTS plus treatment

Thirty nine (52%) patients perceived 50% or more improvement in their condition. However, seven (9.3%) perceived no improvement. When asked about DOTS Plus, majority were found to be satisfied. But around 30% found that treatment makes person incapacitated for any work.

Secondary cases

Twelve (14.8%) patients gave history of secondary case of tuberculosis. Total 17 secondary cases were found. In all patients, the secondary cases

Table 2: Result of culture examination during follow up months

Culture Result	Month of follow up						
	3 (n=86)	**4 (n=82)**	**5 (n=77)**	**6 (n=67)**	**7 (n=67)**	**9 (n=50)**	**12 (n=27)**
Positive	32 (37.2%)	31 (37.8%)	25 (32.5%)	22 (32.8%)	23 (34.3%)	18 (36%)	5 (18.5%)
Negative	54 (62.8%)	51 (62.2%)	52 (67.5%)	45 (67.2%)	44 (65.7%)	32 (64%)	22 (81.5%)
Not available*	6	10	15	26	25	42	65
Total	92	92	92	92	92	92	92

* n= shows no. of patients whose culture results were available at TU at time of visit.
* Not available results were either because patient had expired or defaulted or at the time of visit patient was not eligible for particular month of follow up or result was pending.

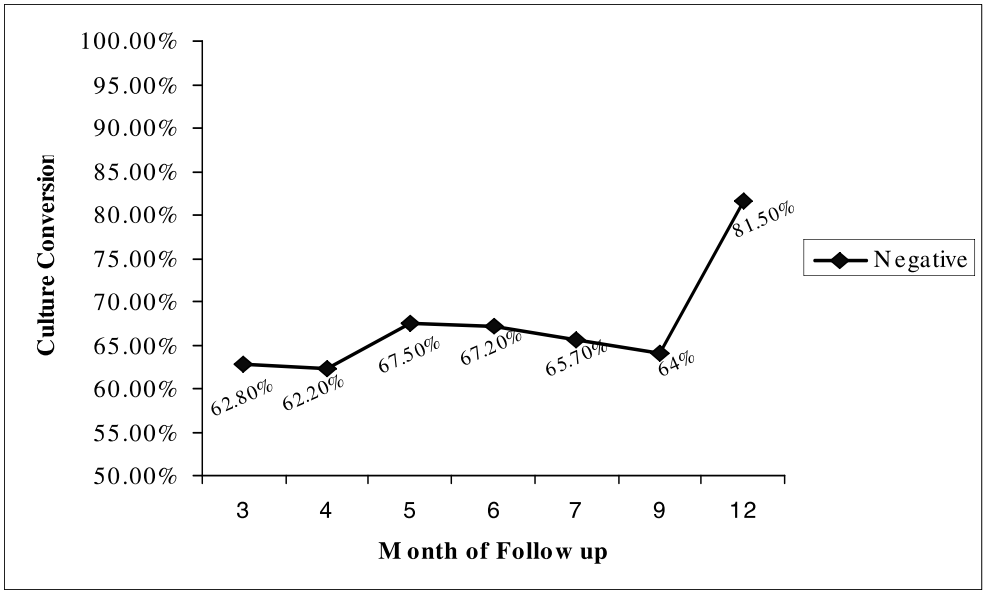


Figure 3: Culture conversion rate in follow up months in available results

were the contacts living in the same premises as that of the patient. No significant difference was found between presence of Secondary case in the family and presence of overcrowding and of adequate ventilation.

Sputum disposal practices

Sixty five (80.2%) patients were used to spit in bathroom or basin and wash it off with water. Use of spit box either plain or containing ash or sand was seen in five (6.2%) and spitting in open ground away from home and covering it with sand was seen in four (4.9%) patients. Seven (8.7%) patients were spitting indiscriminately.

Precautions taken by patients to prevent spread

Most commonly found, though not recommended, was keeping separate utensils for patients in 48 (59.2%) cases either by self or by family member. Practice of covering mouth while coughing/sneezing was found in 37 (45.7%) and keeping children away from self in four (4.9%) patients. No significant difference was found between education of the patient and practice of covering mouth.

DISCUSSION

Present study was conducted with a view to analyze various epidemiological factors and aspects related to DOTS Plus treatment amongst MDR-TB patients put on Category IV during the first year of implementation of DOTS Plus project in city of Ahmedabad. Of the study subjects, more than 2/3rd of cases were males and mean age was about 34 years. Similar finding was found in other studies[13-16]. Unemployment had significantly increased after undergoing Category IV treatment. This seemed to be because of side effects of drugs which made the patients incapacitated for work.

Around 57% of patients were addicted to tobacco and/or alcohol any time during their disease state. Studies in Russia showed alcohol abuse/ dependence[17] and smoking[18] were associated with drug resistance.

About 50% patients gave history of contact with TB case and most of them were family members showing the fact that TB usually spread with close contacts. One striking finding was that in 60% of TB cases, to whom the study subjects were exposed, treatment outcome was death, the reason for the same may be that these persons might have suffered from drug resistant TB which remained undiagnosed. So, contact tracing can be one effective strategy for early detection of cases resulting in favourable outcome.

At the start of Category II, maximum number of patients were defaulters (30.9%) followed by relapse (28.4%), failure (27.2%) and others (13.5%). Afranio L. Kritski *et al*[19] found multi drug resistance in 6% of relapse patients and 33% of failure patients. The main reason for default in this study, found was financial problem.

It was seen that on one hand, referral to RNTCP by private practitioners was hardly 12% and on the other hand most patients preferred private practitioners for illnesses and financial crunch is a major factor for default. These findings suggest that private practitioners must be motivated to refer the patients of lower class to RNTCP so as to prevent default and further wandering of for treatment and consequent development of resistance. Mean number of treatment courses prior to commencement of Category IV was 2.85 times per patient. Similar finding was found in Philippines[14] study.

There were 7.41% patients who defaulted from Category IV, at the time of interview and in 80% the reason being side effects of drugs. Studies conducted in Philippines[14] and Tuberculosis Research Centre[13] showed 14% and 24% defaulter rate and in 69% and in 25%, the reason was adverse events due to drugs respectively.

The symptoms of MDR-TB and drug susceptible TB were found to be the same. Only six (7.4%) patients were having co-morbidity with TB. Of them, 83.3% had Diabetes Mellitus while 16.7% had valvular heart disease. In the Philippines[14] study, around 23% had co-morbidity, of which

around 63% had Diabetes and 7.4% had heart disease.

As compared to other studies[13, 20], present study showed higher proportion of four drug resistance (H, R, S and E) which was about 70%. Only one (1.2%) patient was reactive for HIV as against the finding of Faustini A *et al*[16] which showed that MDR-TB cases were more likely to be HIV positive. However, study by Ruddy M *et al*[20] showed that HIV was not associated with resistance in all patients.

More than 90% (76) of patients experienced side effects, of whom, in 12% (nine) of patients, treatment needed to be modified by stopping the offending drug with/without replacing it with PAS (P-amino salicylic acid) while other patients could continue with the same treatment. The offending drugs in descending order were Cycloserin, Kanamycin, Ofloxacin, Pyrazinamde and Ethionamide. Similar finding was found in the Philippines[14] study and in study by Nathanson *et al*[22].

The culture conversion rate in available results on follow up at the end of third month was 62.8%. In the study of Philippines[14], 90% had converted to sputum culture negative status after three months of treatment. The study by Tuberculosis Research Centre[13] showed 90% culture conversion rate for cured patients by four months.

Majority were found to be satisfied with DOTS Plus treatment.

In 15.0%, secondary cases of tuberculosis were found in household contacts. Study in Uganda[21] found similar finding. However, no significant difference was found between presence of secondary case in the family and presence of overcrowding and of adequate ventilation which may be because of most number of patients living in overcrowded and ill ventilated houses.

Sputum disposal practices showed that indiscriminate spitting was less (8.6%) but other methods were also not safe. A study done by Krishnadas Bhattacharya *et al*[23] found safe sputum disposal practices in 20% and indiscriminate spitting (50.8%). Patients were practising one or the other method/s to prevent spread. The practice of covering mouth during coughing/sneezing was seen in less than 50%. Similar result was found by Krishnadas Bhattacharya *et al*[23] in their study. No significant difference was found between education of the patient and practice of covering mouth. Krishnadas Bhattacharya *et al*[23] found this practice significantly differing between the literates and the illiterates. The finding in the present study may be due to majority of the patients' education up to primary level only.

CONCLUSION

The important points which have come up in the present study are need for motivating private practitioners for referral of patients to RNTCP to improve treatment for drug susceptible cases, provision of psycho-social support and use of patient incentives and enablers to help the patients continue anti-tuberculosis treatment, enhancing contact tracing of the patients and increasing awareness of patients and their family members regarding sputum disposal practices and precautionary measures to prevent the spread. As the present study was confined only to MDR TB cases and there was no comparison group, definite conclusion regarding the factors responsible for development of resistance cannot be drawn. However, based on the findings of this primary evaluation, further study can be framed out and the relationship between various social, behavioural and environmental aspects and drug- resistance can be better examined and understood.

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Original Article

MORPHOLOGICAL ANATOMY OF ACCESSORY FISSURES IN LUNGS

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Summary

***Background*:** Knowledge of the position and grade of accessory fissures and lobes is necessary for appreciation of lobar anatomy and thus locating bronchopulmonary segments.

***Methods*:** Morphological variations of accessory fissures and lobes of the lungs were studied in 40 pairs of lungs from cadavers.

***Results*:** Four left-sided lungs and two right-sided lungs showed accessory fissure in the lower lobe. Only one accessory fissure of left lung belongs to grade-ii and the remaining belongs to grade iii. [According to Craig and Walker's fissural classification]

***Conclusions*:** Awareness regarding accessory fissures and lobes is essential for performing lobectomies, segmental resection, for differential diagnosis and interpreting radiological images. **[*Indian J Tuberc 2012; 59: 28 - 31*]**

Key words: *Accessory Fissure, Dorsal Lobe, Craig and Walker's grade – II fissure, Bronchi.*

INTRODUCTION

Accessory fissures are found occasionally subdividing one of the otherwise normal lobes of the lung. Such fissures are found far more frequently in the right lung than the left, and they also tended to be deeper in the right lung[1] (Fig. 1).

Usually common to observe in the both lungs are notches with incomplete fissures extending for a limited distance on the surface of the lung or even sub-pleural furrows. These are less marked in the adult lung than in that of infant, but do occur. Here also often these notches and sub-pleural furrows are misread as fissures. To differentiate, the fissure corresponds to the inter segmental plane[1] (Fig. 1).

Topographical anatomy is important for radiologist's interpreting skiagrams and surgeons operating on the lungs[2,3].

MATERIAL AND METODS

Forty pairs of lungs from dissection room cadavers of south Indian origin were used for this study. Details regarding accessory fissures and lobes [length and depth] were recorded in a proforma. We have studied the interior by studying the division of bronchial tree starting from the hilum and taken photograph of the bronchial tree.

RESULTS

Left lung

We have observed the presence of an accessory fissure in the lower lobe of four left-sided lungs. In one lung, it was so prominent and started from the posterior border and separates the dorsal lobe from the main lower lobe of left lung (Figures 2 A & B).

Length of the fissure was 8 cms and depth of 4 cms. By dissecting the bronchial tree division from the hilum, we have noticed that apical bronchus and posterior basal bronchus are reaching the dorsal lobe (Figures 3 A & B).

The remaining bronchi (Anterior basal, Posterior basal, Lateral basal) are reaching the remaining portion of left lower lobe. Morphological anatomy of the right lung was normal.

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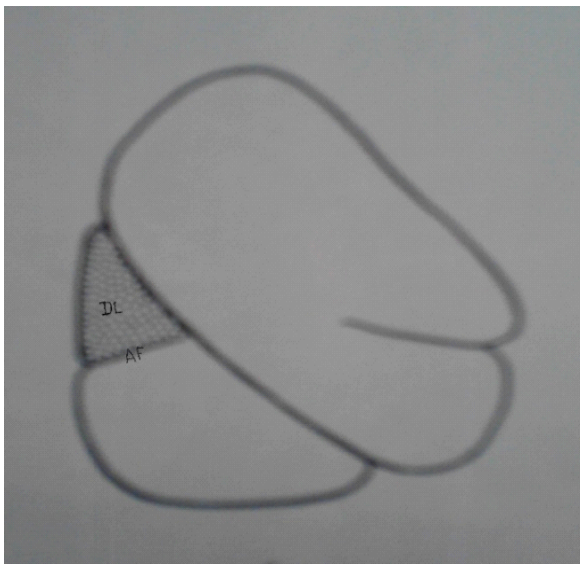

Fig. 1: Accessory Fissure & Dorsal lobe in the Right lower lobe shown in W.Henry hollinshed 1971 pg.no. 72) AF - Accessory Fissure, DL - Dorsal Lobe.

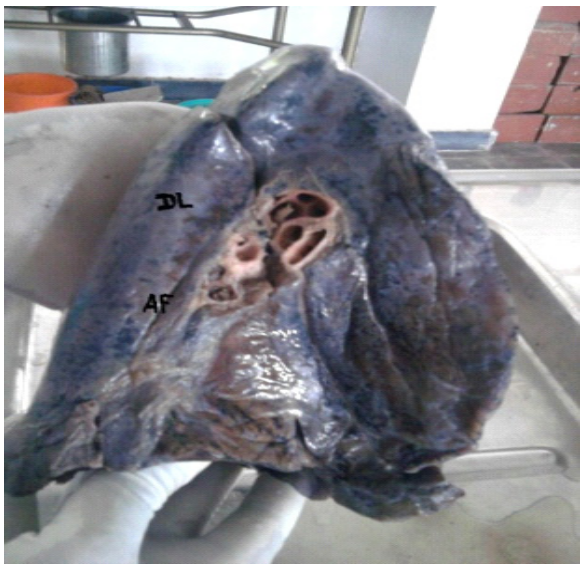

Fig. 2-B: Medial surface of the present case showing Accessory Fissure & Dorsal lobe. AF - Accessory Fissure, DL - Dorsal Lobe.

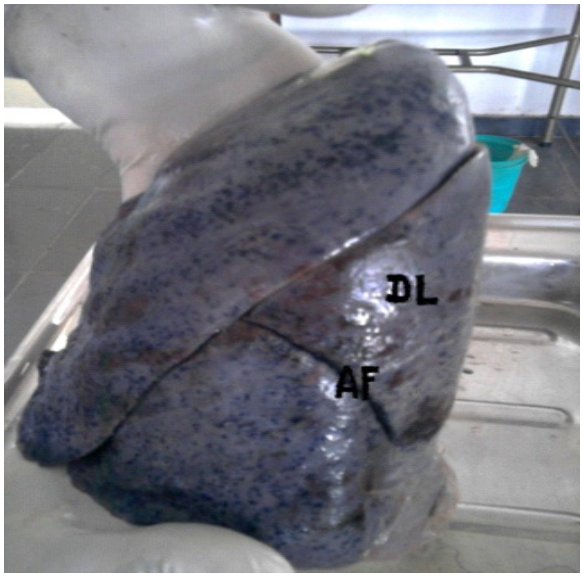

Fig. 2-A: Photograph of Accessory Fissure & Dorsal lobe from the supero lateral surface in present case. AF - Accessory Fissure, DL - Dorsal Lobe.

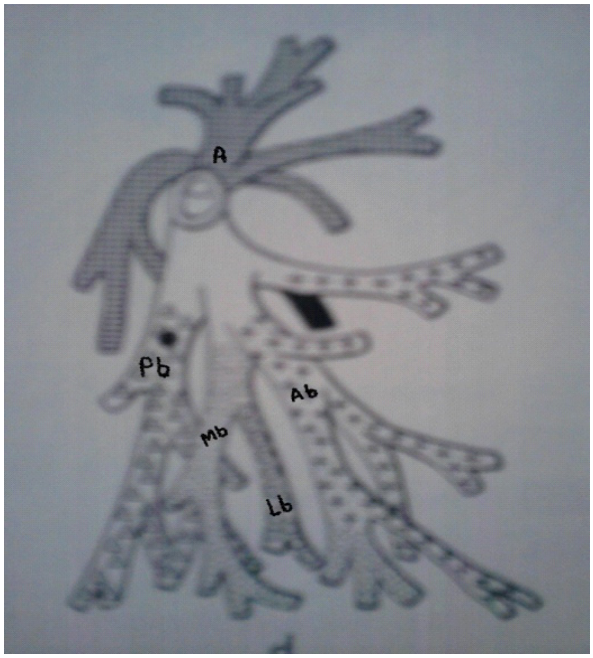

Fig. 3-A: Distribution of segmental bronchi of left lower lobe shown in W. Henry hollinshed. A - Apical, pb - Posterior basal, Mb - Medial basal, Ab - Anterior basal, Lb - Lateral basal

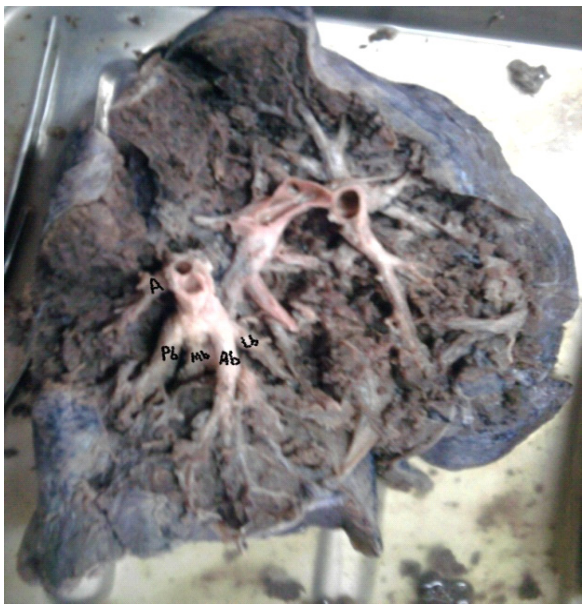

Fig. 3-B: Distribution of segmental bronchi of left lower lobe observed in present case. A- Apical, pb – Posterior basal, Mb – Medial basal, Ab – Anterior basal, Lb – Lateral basal.

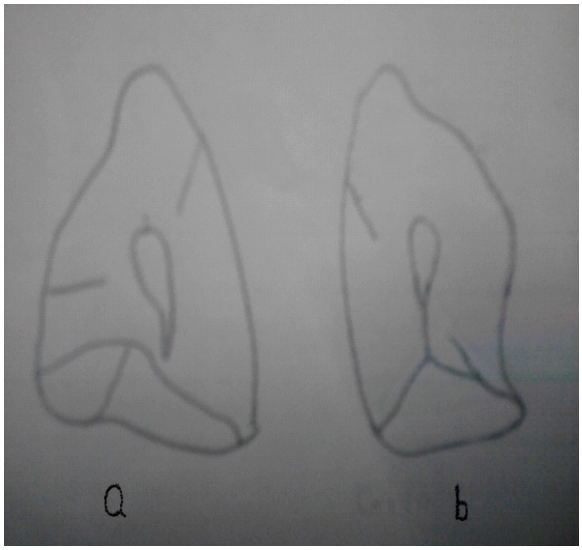

Fig. 4: Grade –II (partial incomplete fissure) According to Craig & Walker's fissural classification. a) Right lung b) Left lung.

In the other lungs, it was less prominent and having the length of 6cms and depth of 1cm.

Right lung

We have observed the presence of a accessory fissure and lobe in the lower lobe of two right-sided lungs. The length and depth of those fissures were 6cms and 1cm.

DISCUSSION

During developing, as the lung grows, the spaces or fissures that separate individual broncho-pulmonary buds/segments become obliterated except along two planes, evident in the fully developed lungs as oblique or horizontal fissures. Absence or incomplete oblique or horizontal fissures could be due to obliteration of these fissures either completely or partially. Accessory fissure could be the result of non-obliteration of spaces which normally are obliterated[4-6].

The nature of the fissure is of great importance in planning operative strategy for thoracoscopic pulmonary resection wherein incomplete fissure may contribute to post-operative air leakage[5,8,9].

In the present study, we have noted an accessory fissure and lobe in the lower lobe of four left-sided lungs and two right-sided lungs. In one of the left lungs, it was measuring about 8 cms in length & depth of 4 cms.

It separates the dorsal lobe clearly from the surface from the remaining part of lower lobe but parenchymal fusion occurring at the base of fissure. According to Craig and Walker's fissural classification, it belongs to grade-ii fissure (Fig. 4).

The accessory fissures present in the lower lobe of remaining lungs were less prominent, having the length and depth of 6cms and 1cm. All these fissures belong to grade iii because they have less depth and by noticing the separation only at the surface.

Craig and Walker have proposed a fissural classification based on the degree of completeness of the fissure. Four stages have been described[7].

Grade i-complete fissure with entirely separate lobes.

Grade ii-complete visceral cleft but parenchymal fusion at the base of the fissure.

Grade iii-visceral cleft evident for a part of fissure.

Grade iv-complete fusion of lobes with no evident fissural line.

The most common fissure observed by Deve was on the diagphramatic surface of the lower lobe, sharply curved towards the vertebral border of the lung from a beginning just anterior to the pulmonary ligament that define the 'cardiac lobe': medical basal segment of the lung. It was identified by Deve in 35% of cases[1].

Deve also reported a partial fissure between the superior and basal segment of the lower lobe occurring in 40 cases on the right lung and 14 on the left lung of 180 infants[1]. Boyden found a transverse fissure in left upper lobe in eight of 100 adult specimens separating the middle lobe of the lung[1]. Sometimes, however, according to Boyden, the fissure does not represent a true separation of the lingular lobe, since the portion demarketed by it may contain anterior segmental bronchi[1].

Incomplete fissure may alter the usual patterns of collapse seen in patients with endobronchial lesions and may also give rise to atypical appearance of pleural effusions[5,8,9]. An incomplete major fissure causes the odd appearances of fluid tracking within the fissure. Incomplete fissures may also alter the spread of disease within the lung. Pneumonia, in particular, lobe is often limited to that lobe alone by the fissures, pneumonia may spread to adjacent lobes through the incomplete fissures. Odd lobar involvement with carcinoma of the lung may be explained on a similar basis[5,8,9].

Table: Comparative incidence of Accessory fissures[1,5].

	S.Meenakshi, Y.Manjunath	**Deve**	**Boyden**	**Present study**
Accessory Fissure present in	Lower lobe	Lower lobe	Upper lobe	Lower lobe
Left lungs	10%	8%	8%	10%
Right lungs	3%	22%	-	5%

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Case Report

PORT SITE TUBERCULOSIS: A CASE REPORT AND REVIEW OF LITERATURE

Pankaj Gupta[1]*, Sandeep Guleria[2]*, Sandeep R Mathur[3] and Ronojoy Ghosh[1]****

(Received on 6.7.2011; Accepted after revision on 9.12.2011)

***Summary*:** A rare case of port site tubercular infection is reported. A young male patient presented, one month after laparoscopic inguinal hernia repair with discharging sinuses at the port sites. Biopsy of the sinus tract showed features of tuberculosis. Excision of sinus tract was done and the patient was started on anti-tubercular therapy, sinuses healed. Probably, the source of tubercular infection was laparoscopic instruments. Proper sterilization of laparoscopic instruments is necessary. **[*Indian J Tuberc 2012; 59:* 32 - 35]**

***Key words*:** Laparoscopy, Port Site, Tuberculosis.

INTRODUCTION

Endoscopy was started around 200 years ago; modern era of laparoscopy was started in 1966 with the development of Hopkins's Rod Lens System [1]. Phillipe Mouret performed the first laparoscopic cholecystectomy in 1987, after which there has been rapid explosion in the field of minimally access surgery[2]. As the number of surgeries undertaken by minimally access approach increased, newer complications like port site metastasis are being encountered by surgeons. Isolated reports of port site tubercular infection are also present in literature[3-9]. The infection has been attributed to improper sterilization of laparoscopic instruments. Most of the cases present as non-healing port site wounds. A case of port site tuberculous infection following Total Extraperitoneal (TEP) repair of inguinal hernia is presented here to add to literature.

CASE REPORT

A 27-year-old male patient presented to us with indirect right side inguinal hernia. Laparoscopic Total Extraperitoneal (TEP) mesh repair was planned. His haemogram and Chest X-Ray were normal. There was no history of chronic cough, fever, loss of appetite, any abdominal complaints or tuberculosis in the past. There was no family history of tuberculosis. Standard three port mesh repair was done and the patient was discharged next day.

He presented with discharging sinuses at the port sites one month after surgery (Figure 1). The patient was started on wide spectrum antibiotic and

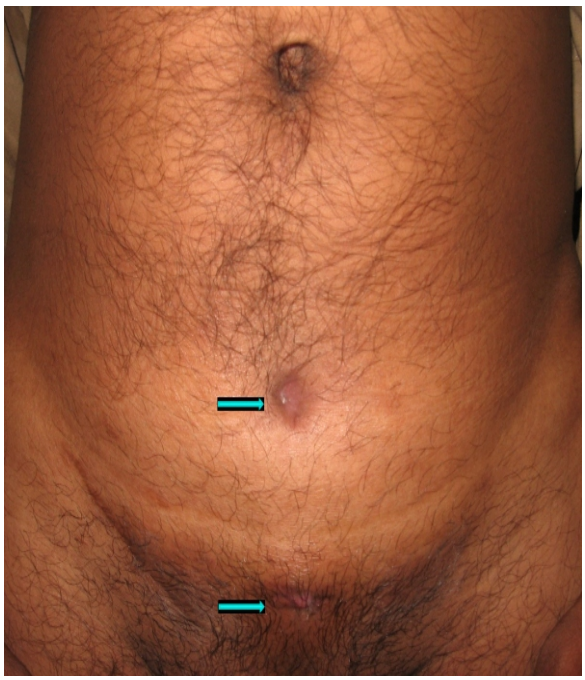

Fig. 1: Non-healing sinuses at the port sites.

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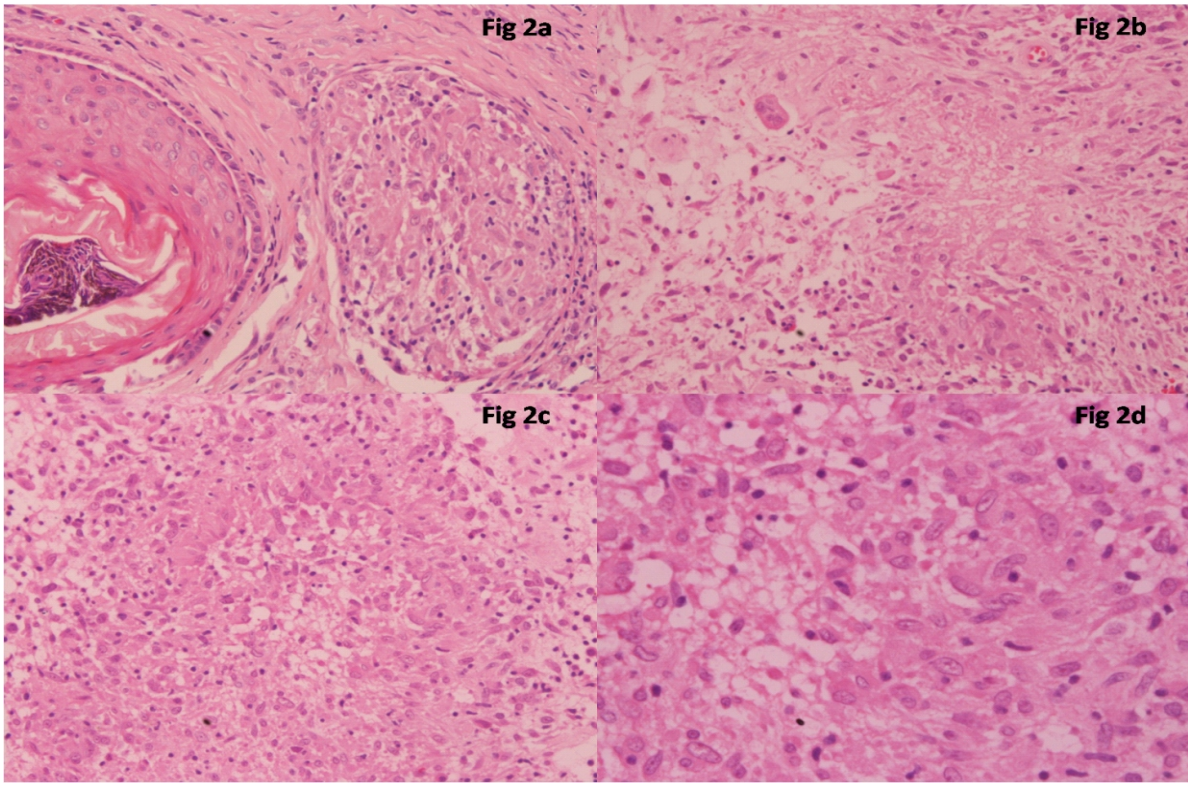

Fig. 2: Photomicrograph showing epithelioid cell granulomas next to adnexal structure (a). Necrotizing granulomas seen in the adjoining tissue (b, c &d) (Hematoxylin & Eosin X 200, 100, 100 & 400 respectively in figs. 2 a, b, c & d)

culture was sent. Culture came out to be sterile and sinuses failed to heal. Biopsy was taken from the wound, which revealed features of necrotizing granulomatous inflammation, suggestive of tuberculosis (Figure 2). Excision of sinus tract was done and four drug antitubercular therapy was started with Rifampicin, Isoniazid, Ethambutol and Pyrizinamide for two months. Rifampicin, Isoniazid was continued for another four months. Wound healed satisfactorily.

DISCUSSION

Port site tuberculosis following laparoscopic surgery is rare, with only isolated case reports in literature. Port site tuberculosis has been reported after various laparoscopic surgical procedures. Bhandarkar *et al* reported a 14-year-old girl who developed port-site tuberculous infection after laparoscopic appendectomy[3]. Leo Francis Tauro *et al* published a case of port site tuberculosis following laparoscopic cholecystectomy. The patient underwent the surgery for chronic calculus cholecystitis. The patient developed multiple discharging sinuses at the port site, two months after surgery. Excision of sinuses was done, histopathological examination of excised sinuses revealed caseous necrosis with Langhan's giant cells, suggestive of tubercular granuloma[4]. Seith A *et al* reported a case of intra abdominal and abdominal wall abscesses of tubercular aetiology, which developed following laparoscopic cholecystectomy[5]. Ramesh *et al* described the clinical features of eight patients who presented with biopsy-proven tuberculosis at the port-site, unassociated with other clinical features of tuberculosis[6]. Three of the eight patients had positive culture for *Mycobacterium tuberculosis*. Five patients underwent laparoscopic gynecological procedures; other three underwent

laparoscopic cholecystectomy, hernia repair and adhesiolysis respectively. Singhi reported a case of port site tubercular infection following laparoscopic hysterectomy[7].

Laparoscopic instruments are the source of infections in most cases[8,9]. Jagadish *et al* reported a case of port site tuberculosis following laparoscopic cholecystectomy. They concluded that laparoscopic instruments were source of tuberculous infection in their case[8]. Sethi *et al* reported port site infection by *Mycobacterium fortuitum* in seven patients who underwent laparoscopic cholecystectomy[9]. All patients developed chronic discharging sinuses. Proper sterilization of laparoscopic instruments is of utmost importance. Most widely used method to sterilize laparoscopic instruments is to immerse the instruments in 2% glutaraldehyde (GTA) for 20 minutes. Two per cent glutaraldehyde solutions range in concentration from 2.4 % to 2.6 % and have variable maximum use lives. According to guidelines of ESGE (European Society of Gastrointestinal Endoscopy) and European Society of Gastrointestinal Endoscopy Nurses and Associates, Glutaraldehyde fail to eliminate all atypical mycobacterium using standard contact times[10]. This is further complicated by the emergence of glutaraldehyde-resistant mycobacterium. Lorena *et al* published that certain stains of mycobacterium are resistant to even high GTA concentrations (up to 7%), which proves that GTA is non-effective against specific rapidly growing mycobacteria and should be substituted by orthophthaldehyde (OPA) and peracetic acid (PA) based solutions for high level disinfection (HLD)[11]. But the efficacy and the properties of these new disinfectants need to be evaluated further. Instruments need to be pre-cleaned properly before immersing in GTA for disinfection. Instruments should be dismantled and all blood clots, tissues, etc., should be removed under running water before sterilization. As, after washing, some amount of water goes into GTA solution, its concentration decreases, making it less efficient. It is imperative that solution should be regularly changed and instruments should be dried before immersion in GTA solution. Autoclave is the best method of sterilization. All metallic instruments should be autoclaved.

There are some reports in literature which suggest that port site tuberculosis may be caused by endogenous abdominal tuberculosis. Narayanan *et al* reported a case of port site tuberculosis in a young female. Diagnostic laparoscopic was done for primary infertility, which revealed scattered tubercles in the peritoneum. Biopsy of tubercles revealed tuberculosis. The patient subsequently developed chronic discharging sinuses from the port site, which were later proved to be due to tuberculosis [12]. They suggested that port site wound was caused by implantation of tubercular bacterium.

High index of suspicion is required for diagnosis of port site tuberculosis. Most patients develop chronic discharging sinuses and/or non-healing of port site wound, as occurred in our case. S.K Jain *et al* reported a case of young man who developed parietal swelling at the site of mid clavicular port following laparoscopic cholecystectomy[13]. Microscopic examination of aspirated material from the swelling revealed, chronic granulomatous inflammatory material with Langhan's giant cells, suggestive of tuberculosis. Excision of sinus tract/ non-healing port site wound with four drug antitubercular therapy is mainstray of treatment.

CONCLUSIONS

Utmost care should be taken and proper technique should be followed for sterilization of laparoscopic instruments. Instruments should be dismantled and thoroughly cleaned before sterilization. Use of glutaraldehyde should be discouraged and instead autoclaving should be done.

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SLEEPCON 2012

National Conference on Sleep Disorders, organized by Department of Pulmonary Medicine, Government Medical College & Hospital, Chandigarh, under the auspices of Indian Sleep Disorder Association, will be held in Chandigarh from 6th to 8th April, 2012. For updated information, please visit: www.gmch.gov.in/conference.

Case Report

PRIMARY TUBERCULAR OSTEOMYELITIS OF MANDIBLE: RARE PRESENTATION OF A COMMON DISEASE

Suresh Kumar[1], Rakesh Kumar[2] and Meenu Singh[3]

(Received on 6.7.2011; Accepted after revision on 9.12.2011)

***Summary*:** Secondary tuberculosis of mandible is an uncommon complication of primary tuberculosis elsewhere in the body, most frequently, in the lungs. Primary tuberculosis of the mandible is a very rare entity, of which only eight cases have been reported in literature till date. A case of primary tuberculosis of mandible in a 9-year-old girl is presented here. **[*Indian J Tuberc 2012; 59:* 36 - 38]**

***Key words*:** Primary, Tubercular osteomyelitis, Mandible

INTRODUCTION

Infection with *Mycobacterium tuberculosis* usually involves lungs, but any part of the body can be affected. Skeletal tuberculosis accounts for 6.6% of extra pulmonary tuberculosis and jaw involvement occurs in less than 2% of the latter[1]. Flat bones of skull and mandible are rarely affected. Till date, only eight cases of primary tuberculosis of mandible have been reported[2-8]. In an attempt to highlight a rare but significant presentation, we document a case of tubercular osteomyelitis of mandible without pulmonary involvement.

CASE REPORT

A 9-year-old girl presented with progressively increasing swelling of the left jaw and intermittent fever for three months associated with painful movements of jaw. She received oral antibiotics for two weeks without any improvement. She was vaccinated with BCG and had no prior or family history of tuberculosis.

On examination, her weight was 20 kgs (<5th centile), had mild pallor and left submandibular lymphadenopathy. Local examination revealed a 5x6 cms sized swelling on the left side of face extending horizontally from anterior end of masseter to angle of mandible and vertically from tragus to lower border of mandible which was smooth, cystic, fluctuant, tender with no erythema, warmth, sinus, or discharge (Figure 1). Examination of oral cavity and systemic examination was normal. Laboratory findings included: Hb -1.55 µmol/L, WBC counts - 9.5 ×10^3/µL, platelet count - 660 ×10^9/L, blood sugar - 5.39 mmol/L and Mantoux test was positive (12 mm). Gastric lavage did not show acid-fast bacilli (AFB). Chest radiograph and

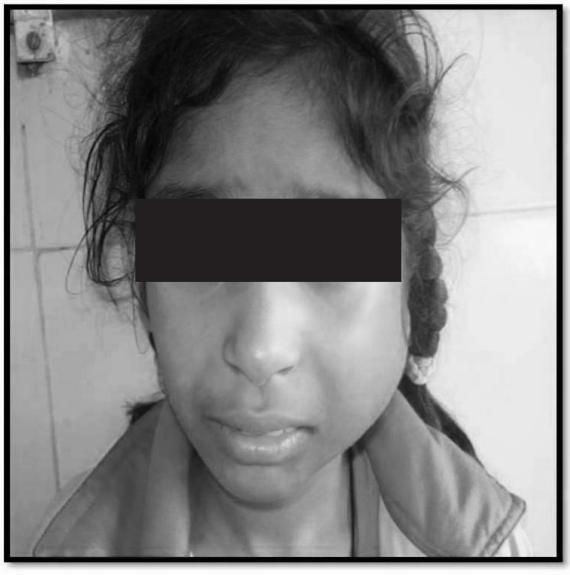

Figure 1: Swelling over left jaw.

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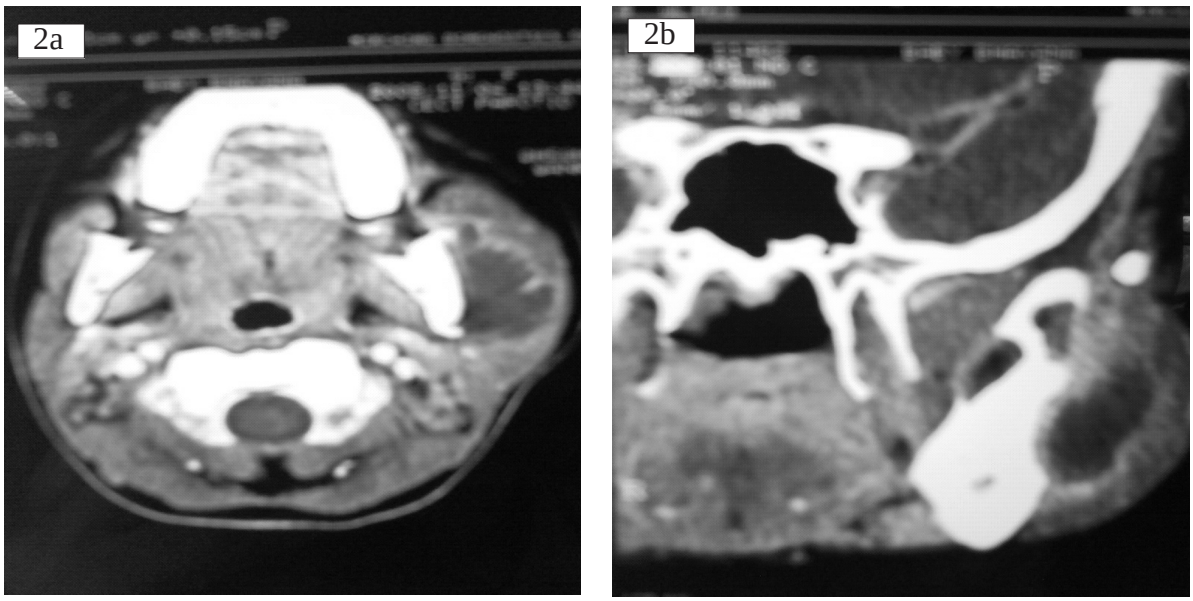

Figures 2a and 2b: CECT of mandible (axial and coronal sections) showing lytic expansile soft tissue attenuation lesion with overlying cortical break of coronoid process of mandible on left side along with erosion of left mandibular condyle and ramus with periosteal reaction. Surrounding muscles of masticator space, parapharyngeal space and infratemporal fossa are bulky. There is loculated peripherally enhancing fluid collection in left masticator.

CECT chest was unremarkable. HIV screening test was negative. CECT of mandible revealed lytic expansile soft tissue attenuation lesion with overlying cortical break of coronoid process of mandible on left side along with erosion of left mandibular condyle and ramus with periosteal reaction (Figures 2a &2b). There was a 2.4 x 1.8 cms loculated peripherally enhancing fluid collection in left masticator space. Aspiration yielded 15 ml of thick, purulent material which, on microscopic examination, revealed amorphous material devoid of any cellular elements. Bacterial culture was sterile. Surgical drainage of pus and excision of coronoid process was done. Intra-operative findings showed enlarged coronoid process due to reactive bone formation and lateral side of it was eroded and replaced with necrotic granulation tissue. Histopathological examination showed multiple epithelioid cell granulomas within the marrow spaces, along with multinucleated giant cells, areas of caseation necrosis and lymphocytic infiltrates. Ziehl Neelsen (ZN) stain for AFB was positive.

Diagnosis of primary tubercular osteomyelitis of mandible was considered and patient was started on antitubercular chemotherapy. After two months of therapy, she improved markedly with decrease in size of swelling. She was under regular follow up and completed nine months of ATT (2 HRZE+ 7HR). On review, six months after completion of treatment, she remains well and has no signs of recurrence of disease.

DISCUSSION

Primary tuberculosis of mandible is extremely rare and generally occurs in younger patients, whereas secondary lesions are more common and are seen mostly in elderly patients[9]. Tuberculosis of mandible is mostly secondary to a primary lesion elsewhere in body[5]. Previously, Gupta *et al* from our centre reported a case of primary tuberculosis of mandible in a 9-year-male child[5].

The diagnosis of tuberculosis of mandible is very difficult as there are no specific signs pathognomonic of infection[2]. The diagnosis must be established by histopathological examination of the tissue with demonstration of organism in the lesion coupled with culture[2]. PPD test may give false negative results. Chest radiograph and sputum culture for AFB should be performed. CT chest is more sensitive than plain radiography. High resolution CT may reveal occult abscesses, pathological cavities, and the extent of disease[10].

In a patient of mandibular tuberculosis, evidence of primary lesion can be accepted only if a history and medical evidence of pulmonary tuberculosis are excluded by radiographs and laboratory tests[8]. In our patient there were no indications in history or in laboratory or radiographic findings that were suggestive of pulmonary tuberculosis.

Primary treatment for tuberculosis of mandible is long term anti-tubercular therapy up to nine months[10]. Local treatment in the form of incision and drainage of infected material together with sequestrectomy or saucerisation should be carried out when required[2].

CONCLUSION

Even though tuberculosis of mandible is rare, it must be kept as an important differential diagnosis when routine antibiotic treatment fails to bring improvement in lesions of mandible, especially in developing countries where TB is very common. Histopathological examination of the tissue is essential to establish the diagnosis. Therapy must emphasize rational anti-tubercular treatment in addition to local treatment. Prognosis of primary tuberculosis of mandible is excellent, and appropriate treatment can lead to reversal of all destructive bony changes.

ACKNOWLEDGEMENTS

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Case Report

LINGUAL TUBERCULOSIS

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(Received on 6.7.2011; Accepted after revision on 9.12.2011)

***Summary*:** Oral tuberculosis is very rare and when present they are usually secondary to pulmonary tuberculosis. Tuberculous lesions of the tongue have become so infrequent that they are virtually a forgotten disease entity and may pose a diagnostic problem. The case reported in this paper emphasizes the importance of including tuberculosis in the differential diagnosis of any chronic oral ulcer. The low number of oral infections by *M. tuberculosis* could be due to underreporting. **[*Indian J Tuberc 2012; 59:* 39 - 41]**

Key words: Tuberculosis, Tongue Ulcer.

INTRODUCTION

Tongue tuberculosis is very rarely described in the literature. It was reported that it occurred in only one of 5,094 patients who were diagnosed as having pulmonary tuberculosis. It can be primary with no evidence of involvement of other organs, especially the lungs, or, more commonly, secondary to pulmonary tuberculosis. The intact oral mucosa is believed to be resistant to tubercular infection due to cleansing action of saliva, presence of saprophytes, antagonism of the striated musculature to bacterial invasion and the thickness of a protective epithelial covering. Predisposing factors include poor oral hygiene, trauma, tobacco, irritation, dental extraction, pyogenic foci and leukoplakia.

CASE REPORT

A 33-year-old female patient was admitted to our hospital with a painful ulcer on the tongue. She was also suffering from gradual loss of weight and generalized weakness. There was no history of trauma, toothache, cough, fever, blood stained sputum or night sweats. Physical examination was unremarkable except for the presence of an ulcer of about 2 cm x 3 cm in size over right lateral border of the tongue. Margin of the ulcer appeared to be undermined and base was covered with pale slough (Fig. 1).Teeth adjacent to the ulcer were sharp. On palpation, the ulcer was tender to touch and margin was indurated. Laboratory investigations revealed 10.5 gm haemoglobin, 8100 total leucocyte count and an erythrocyte sedimentation rate of 20 mm/ hour. Biochemical parameters were within normal limits. Chest X ray was normal (Fig. 3). HIV test was negative. There was no evidence of anyother immunodeficiency syndrome. A provisional diagnosis of malignant ulcer was made. A small biopsy from the margin and centre of the ulcer was performed under local anesthesia and sent for the histopathological examination (Fig. 2). Surprisingly, histopathology report revealed feature of granulomatous inflammation with areas of caseation necrosis. The granulomas were composed of epithelioid cells, Langhan's giant cells and lymphocytic infilration suggestive of tuberculosis (Fig. 2). As the biopsy report showed tuberculosis, patient was further investigated. Tuberculin test was positive (18 mm infiltration). A week after starting antituberculous therapy (rifampicin 600 mg/day, isoniazid 300 mg/day, pyrazinamide 1500 mg/day, ethambutol 1500 mg/day), the lesions started to regress and the ulcers healed completely in one and a half months.

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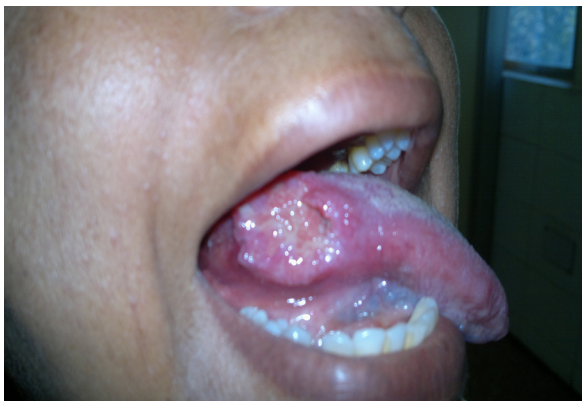

Fig. 1: Clinical picture of tongue ulcer with undermined edges

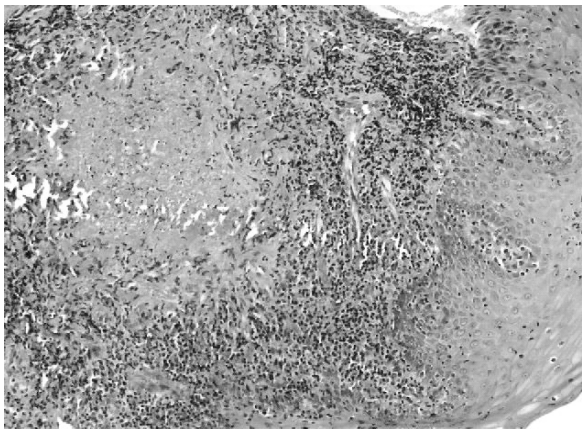

Fig. 2: Histological picture of Lingual tuberculosis

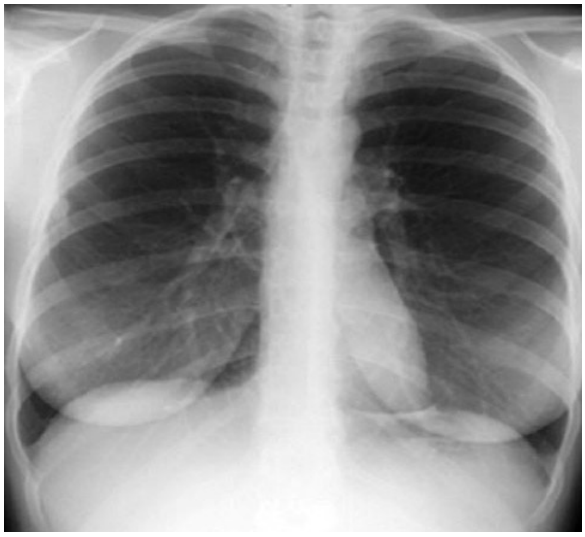

Fig. 3: Chest X-ray - PA view

DISCUSSION

According to the views predominating at the world, both primary and secondary tuberculosis of tongue and oral cavity are rare and occur in less than 0.2% of all cases of tuberculosis. Morgagni(1761) described the first case of lingual tuberculosis. Tongue is the most commonly affected structure of oral cavity. Other sites are floor of mouth, palate, gingival, lips, mucobuccal folds, inflammatory foci adjacent to teeth or extraction sites. It may occur as primary or secondary to tuberculosis of other organs. Tubercular infection of the tongue usually occurs due to contact with the infected sputum (Ghose, 1966) but it may also occur by blood spread, lymphatic spread or by direct contamination from the neighbouring tuberculous focus in the oral cavity. Tuberculosis of tongue is more common among males than females. Secondary tuberculosis of tongue is usually observed in patients aged over 30 years. Primary TB, on the other hand, is very unusual and is seen in younger patients; may be associated with cervical lymphadenopathy[1,2]. Tuberculosis of tongue may occur in various forms as ulcers, nodule, fissures, plaques or vesicles. The other oral manifestations of TB can be indurated soft-tissue lesions or even lesions within the jaw that may be in the form of TB osteomyelitis or simple bony radiolucencies. The lesions are almost always painful. The most frequently occurring lesion is an ulcer, characterized by irregular edges with minimal induration. The base of an ulcer may be granular or covered with pseudomembrane. The dorsal surface of the tongue is affected most commonly followed by the palate, buccal mucosa and lips. The salivary glands, tonsils and uvula also are involved frequently. Secondary lesions of the mandibular ridge (alveolar mucosa) are extremely rare[3].

The pathogenesis of oral TB usually is self-inoculation with infected sputum, resulting from the constant coughing up of bacteria that seed themselves in the oral tissue along their line of discharge through the mouth. Haematogenous spread of TB bacteria also occurs. Additionally, direct inoculation of *M. tuberculosis* also has been reported. It is believed that an intact squamous epithelium of the oral mucosa serves as a barrier to the penetration of TB bacilli[4-6]. This has been attributed to the cleansing action of

saliva; the presence of salivary enzymes, tissue antibodies and oral saprophytes; and the thickness of the protective epithelial covering. However, small tears in the mucosa caused by chronic irritation or inflammation may be favourable sites for the colonization of organisms even if the onset is by hematogenous spread, since injured or inflammed tissues tend to localize bloodborne bacteria[7]. The differential diagnosis of such lesion includes malignancy, foreign body granulomas, major apthus ulcer, syphilis, sarcoidosis and fungal infection. The present patient had only painful ulcer on the tongue and there was no systemic effects of the tuberculosis like cough and haemoptysis. It was suspected that the patient's sharp teeth caused an ulcer on the tongue which subsequently infected by sputum borne tubercular bacilli. **Patients with tongue tuberculosis respond well to antituberculous therapy because tongue is highly vascular[8]. In most cases, tongue lesions heal completely within a few months.**

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STATUS REPORT ON RNTCP*

RNTCP has continued to achieve the twin objectives of NSP case detection and treatment success rate at the national level during the third quarter, 2011 (Figure). With this, it is evident that the programme, while sustaining its past achievements, is progressing satisfactorily towards achieving the TB related Millennium Development Goals, in terms of achieving the programme objectives.

RNTCP performance in third quarter 2011

During the quarter, over two million suspects were examined, 2,41,957 sputum positive cases were diagnosed, and 390,770 TB cases were registered for treatment. The annualized total case detection rate is 131 cases per 100,000 population. With a total of 163,141 new smear positive cases being registered for treatment, the new smear positive TB case notification rate (annualized) for the third quarter 2011 is 55 per lakh population. In addition to this, 88,222 new smear negative cases, 58,534 new extra pulmonary cases, 54,452 smear positive re-treatment cases and 26,875 re-treatment Others' were also registered for treatment in this quarter. The treatment success rate amongst the new smear positive Pulmonary TB cases registered in the third quarter 2010 is 87.8% and the sputum conversion rate of patients registered during second quarter, 2011 is 90%. The default rates among NSP (5.8%), NSN (7%) and re-treatment cases (14.3%) continue to show the declining trend over the past several quarters.

Major activities during the quarter

Programme review Supervision, Monitoring and Training

Fourteen states were reviewed for their performance in RNTCP on a one-to-one basis along with their activity plans to improve programme

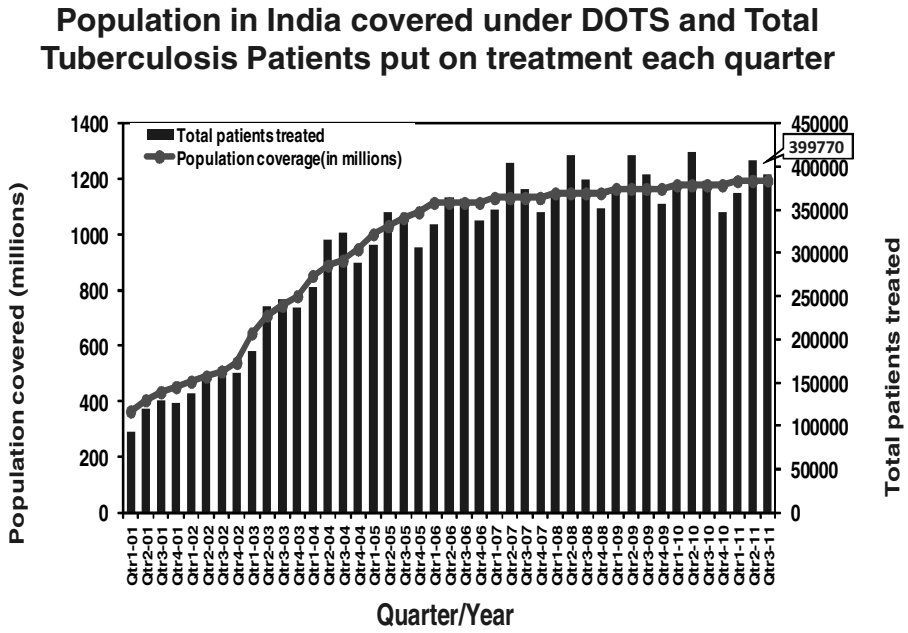

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Table: Performance of RNTCP Case Detection (2011, third quarter), Smear Conversion (2011, second quarter), and Treatment Outcomes (2010, third quarter)

State	Population (in lakh) covered by RNTCP[1]	No. of suspects examined	Suspects examined per lakh population	Rate of change in suspects examined per lakh population (compared to same quarter in previous year)	No of Smear positive patients diagnosed[2]	Suspects examined per smear positive case diagnosed	Rate of change in suspects examined per s+ case diagnosed (compared to same quarter in previous year)	Annualized smear positive case notification rate (reported by RNTCP DMCs)	Annualized smear positive case notification rate [from CFR: sm + cases (NSP + Rel + TAD) * 4 / Pop]	Total patients registered for treatment[3]	Annualized total case notification rate	Annualized new smear positive case notification rate	Annualized new smear negative case notification rate	Annualized new extra pulmonary case notification rate	Annualized previously treated case notification rate
Andaman & Nicobar	5	1062	215	-13%	82	13	18%	66	70	217	176	51	45	53	28
Andhra Pradesh	847	140255	166	-9%	19231	7	-9%	91	78	28077	133	59	29	16	28
Arunachal Pradesh	13	2808	217	-3%	351	8	-20%	108	83	579	179	61	35	33	48
Assam	314	38670	123	-3%	6079	6	6%	77	68	10223	130	56	32	17	25
Bihar	977	97383	100	12%	11655	8	4%	48	43	19637	80	35	23	5	16
Chandigarh	14	4318	300	2%	630	7	14%	175	91	685	191	66	20	66	38
Chhattisgarh	243	28044	116	-4%	3270	9	-5%	54	49	6771	112	43	40	14	14
D & N Haveli	4	754	213	31%	76	10	42%	86	67	107	121	52	25	21	23
Daman & Diu	3	863	320	36%	69	13	25%	102	43	81	120	39	40	22	19
Delhi	195	40255	207	2%	6220	6	8%	128	106	13153	270	72	45	88	65
Goa	18	3992	226	-2%	326	12	11%	74	58	516	117	42	16	33	26
Gujarat	590	111975	190	-9%	14930	8	-6%	101	86	18913	128	60	14	16	38
Haryana	254	46970	185	22%	6507	7	20%	102	86	10136	159	58	28	30	43
Himachal Pradesh	68	18688	275	3%	1917	10	8%	113	99	3433	202	69	34	49	49
Jammu & Kashmir	117	23114	197	28%	2238	10	3%	76	72	3415	117	57	15	24	20
Jharkhand	315	40265	128	-5%	5912	7	-3%	75	70	10121	129	59	37	9	24
Karnataka	594	142831	240	8%	11747	12	1%	79	65	18247	123	50	26	21	26
Kerala	346	87020	252	2%	3658	24	3%	42	36	6314	73	30	16	17	10
Lakshadweep	1	253	333	118%	3	84	122%	16	16	4	21	11	0	5	5
Madhya Pradesh	722	108717	151	14%	14497	7	7%	80	68	24437	135	52	42	14	27
Maharashtra	1127	194599	173	2%	19115	10	2%	68	62	35177	125	47	27	21	29
Manipur	24	3655	149	2%	388	9	5%	63	58	885	145	50	35	35	25
Meghalaya	26	6395	244	5%	673	10	19%	103	84	1503	229	65	57	56	48
Mizoram	10	2234	223	-7%	208	11	-33%	83	75	600	239	53	54	84	48
Nagaland	22	4074	181	-3%	498	8	2%	89	80	1020	181	60	38	42	42
Orissa	408	52025	128	-10%	6883	8	-6%	68	61	11980	118	51	28	21	17
Puducherry	14	5731	412	-2%	660	9	9%	190	54	367	106	42	20	27	17
Punjab	277	45662	165	8%	5636	8	16%	81	75	9927	143	54	27	32	30
Rajasthan	678	109432	161	4%	18963	6	15%	112	93	29028	171	64	44	22	40
Sikkim	6	1835	300	-17%	167	11	-8%	109	98	424	277	71	60	81	65
Tamil Nadu	674	156291	232	-4%	11237	14	-1%	67	62	19791	117	48	28	23	19
Tripura	36	5261	145	-6%	517	10	-7%	57	52	756	84	46	14	13	10
Uttar Pradesh	2008	327494	163	9%	48738	7	-4%	97	88	75079	150	70	35	18	27
Uttarakhand	99	18995	191	6%	2724	7	0%	110	84	4014	161	58	36	26	41
West Bengal	895	145616	163	-3%	16152	9	0%	72	64	25153	112	52	20	19	21
Grand Total	**11944**	**2017536**	**169**	**2%**	**241957**	**8**	**4%**	**81**	**71**	**390770**	**131**	**55**	**30**	**20**	**27**

1 Projected population based on census population of 2001 is used for calculation of case-detection rate. 1 lakh = 100,000 population

2 Smear positive patients diagnosed, include new smear positive cases and smear positive retreatment cases, data from DMCs

3 Total patients registered for treatment, include new sputum smear positive cases, new smear negative cases, new extra-pulmonary cases, new others ,relapse,failure,TAD and retreatment others

State	Annualized previously treated smear positive case notification rate	No (%) of pediatric cases out of all New cases		3 month conversion rate of new smear positive patients	Success rate of new smear positive patients	3 month conversion rate of retreatment patients	No (%) of all Smear Positive cases started RNTCP DOTS within seven days of diagnosis		No (%) of all Smear Positive cases registered within one month of starting RNTCP DOTS treatment		No (%) of all cured Smear Positive cases having end of treatment follow-up sputum done within seven days of last dose		No (%) of cases (all forms of TB) registered receiving DOT through a community volunteer		Proportion of all registered TB cases with known status	Proportion of TB patients known to be HIV infected among tested	Proportion of TB patients known to be HIV infected among registered	Proportion of HIV infected TB patients put on CPT(RT report)	Proportion of HIV infected TB patients put on ART (RT report)
Andaman & Nicobar	22	10	5%	94%	85.3%	71%	85	94%	79	88%	73	97%	52	24%	11%	0%	0%		
Andhra Pradesh	20	1048	5%	92%	89.4%	75%	15158	90%	16367	97%	11535	83%	23351	83%	87%	11%	9%	89%	45%
Arunachal Pradesh	25	53	13%	90%	89.3%	78%	244	87%	253	91%	202	91%	177	31%	71%	0%	0%		
Assam	13	417	5%	86%	83.0%	66%	4714	87%	5108	94%	2992	74%	3534	35%	32%	1%	0%	38%	77%
Bihar	8	1118	7%	86%	88.7%	71%	9158	87%	10305	97%	5246	72%	13563	69%	11%	4%	0%	21%	48%
Chandigarh	29	55	10%	91%	88.1%	72%	308	90%	341	99%	294	92%	106	15%	99%	1%	1%	100%	100%
Chhattisgarh	7	320	5%	88%	86.9%	72%	2658	88%	2936	97%	1905	83%	3365	50%	14%	6%	1%		
D & N Haveli	15	7	8%	86%	81.6%	65%	54	92%	59	100%	35	95%	19	18%	34%	0%	0%		
Daman & Diu	7	2	3%	83%	100.0%	78%	28	90%	31	100%	27	100%	25	31%	86%	3%	2%	0%	0%
Delhi	39	1281	13%	88%	85.4%	70%	4858	90%	5353	99%	3594	90%	1186	9%	66%	2%	1%	79%	69%
Goa	18	29	7%	89%	80.8%	68%	230	87%	258	97%	204	96%	82	16%	97%	6%	6%	100%	49%
Gujarat	27	725	5%	91%	88.0%	67%	11796	92%	12655	98%	9516	89%	10691	57%	91%	5%	4%	97%	72%
Haryana	31	467	6%	89%	88.1%	73%	5046	89%	5286	93%	3357	82%	2809	28%	94%	1%	1%	44%	39%
Himachal Pradesh	33	177	7%	91%	90.2%	81%	1652	96%	1673	97%	1333	90%	371	11%	31%	2%	1%	75%	88%
Jammu & Kashmir	17	181	6%	91%	90.7%	81%	2108	97%	2145	99%	1410	96%	427	13%	10%	1%	0%	25%	75%
Jharkhand	11	451	5%	91%	89.9%	79%	4693	84%	5512	99%	3109	69%	6338	63%	22%	2%	0%	3%	70%
Karnataka	18	1179	8%	88%	82.9%	64%	8581	86%	9571	96%	5501	80%	8980	49%	93%	13%	12%	100%	74%
Kerala	7	751	14%	84%	83.1%	68%	2776	86%	2866	89%	1871	73%	4006	63%	64%	2%	1%	47%	68%
Lakshadweep	5	0	0%	100%	100.0%	0%	3		3		4	0%	0	0%	0%		0%		
Madhya Pradesh	17	2353	12%	91%	89.5%	68%	11007	88%	11494	92%	7130	75%	14683	60%	16%	2%	0%	29%	67%
Maharashtra	16	1870	7%	89%	87.0%	66%	15212	85%	16900	94%	10712	81%	11175	32%	80%	10%	8%	96%	59%
Manipur	9	51	7%	88%	90.7%	70%	350	96%	347	95%	257	83%	474	54%	48%	12%	6%	56%	49%
Meghalaya	27	231	19%	85%	81.9%	60%	552	91%	576	95%	366	86%	832	55%	12%	1%	0%	100%	0%
Mizoram	26	98	20%	90%	88.2%	76%	195	99%	190	96%	108	96%	121	20%	74%	12%	9%	89%	49%
Nagaland	22	139	18%	93%	89.8%	84%	342	74%	364	79%	319	78%	389	38%	51%	10%	5%	85%	53%
Orissa	10	580	6%	88%	86.4%	68%	5097	82%	6091	97%	3414	68%	8602	72%	22%	3%	1%	20%	10%
Puducherry	13	26	8%	90%	86.8%	67%	154	80%	162	84%	136	96%	0	0%	63%	0%	0%	100%	17%
Punjab	22	502	6%	90%	88.0%	75%	4920	93%	5166	98%	4344	92%	2740	28%	69%	2%	1%	77%	49%
Rajasthan	31	1123	5%	92%	89.9%	77%	13282	82%	15514	96%	10892	78%	3938	14%	26%	1%	0%	69%	54%
Sikkim	37	39	13%	78%	73.6%	56%	153	92%	119	72%	122	98%	173	41%	9%	3%	0%		
Tamil Nadu	15	1085	7%	90%	86.0%	69%	8690	82%	10220	97%	6593	81%	5194	26%	89%	7%	6%	84%	59%
Tripura	8	17	3%	86%	87.5%	69%	371	76%	476	97%	284	71%	346	46%	31%	1%	0%		
Uttar Pradesh	20	3948	6%	91%	89.5%	78%	40104	90%	44319	99%	27580	85%	52982	71%	17%	1%	0%	24%	30%
Uttarakhand	27	242	8%	90%	86.4%	73%	1899	89%	2101	99%	937	60%	2393	60%	46%	1%	0%	67%	33%
West Bengal	14	980	5%	88%	85.4%	66%	11861	80%	13969	94%	9808	82%	6736	27%	47%	2%	1%	53%	51%
Grand Total	**18**	**21555**	**7%**	**90%**	**87.8%**	**72%**	**188339**	**87%**	**208809**	**96%**	**135210**	**81%**	**189860**	**49%**	**48%**	**6%**	**3%**	**90%**	**59%**

performance in the respective states during July-September 2011. The status of PMDT services for Multi-Drug Resistant TB was reviewed in Guwahati in July 2011 for all the North-Eastern states. Central Internal Evaluation of Goa was conducted by Central TB Division (CTD) and a few state internal evaluations of various districts were also undertaken.

Progress in accreditation of Intermediate Reference Laboratories (IRL)

RNTCP has accredited 30 Culture and DST laboratories in the country which include four national reference laboratories, 15 intermediate reference laboratories and 10 laboratories from other sectors like medical colleges, NGOs and private sectors, the other laboratories are in different stages of accreditation. The Line Probe Assay (LPA) has been introduced in the programme and two NRLs, three IRLs and three medical college laboratories have been accredited and one laboratory in private sector with liquid culture diagnostics has been accredited to deliver the services. Twentieth national laboratory Committee meeting was held in July 2011.

Progress in the Programmatic Management of Drug Resistant TB (PMDT) services

Services for programmatic management of drug resistant TB (PMDT) are now available in 211 districts covering a population of 412.6 million (35%) in 24 states/UTs. At the end of third quarter 2011, a total of 5810 MDR TB patients were initiated on treatment through 38 DOTS Plus sites in these states/UTs. In third quarter 2011, central level PMDT appraisals were conducted in Orissa (11 districts), Andhra Pradesh (seven districts), Madhya Pradesh (10 districts), Chandigarh, Goa (two districts), Uttarakhand (two districts), Jammu & Kashmir (two districts), Rajasthan (five districts), Daman Diu (one district), Dadra Nagar Haveli (one district), Manipur (two districts), Mizoram (two districts), Nagaland (two districts), Chhattisgarh (three districts), Assam (two districts), Arunachal Pradesh (four districts), Meghalaya (two districts), Tripura (two districts), Sikkim (one district), Jharkhand (seven districts), Bihar (two districts) and Punjab (three districts). Andaman & Nicobar, Arunachal Pradesh, Jammu & Kashmir, Manipur, Mizoram, Nagaland and Uttarakhand states rolled out services in their first phase districts during the quarter. Other states are in various stages of preparatory activities for rolling out PMDT services.

Four batches of national training in PMDT were conducted at Gujarat (two batches), Andhra Pradesh (two batches) and Kerala (one batch) in this quarter.

Progress in PPM and ACSM activities

All the Zonal Task Forces were conducted except the North East which was cancelled subsequent to the natural disaster in Sikkim. Currently, 291 Medical Colleges are offering RNTCP services. In 2010-11, 95272 smear-positive TB cases, 49,114 smear-negative TB cases and 83,738 extra-pulmonary TB cases were diagnosed at medical colleges and referred for treatment; altogether, this accounts for about 11% of NSP cases and 15% of all cases diagnosed and registered for treatment in the country.

Progress in TB HIV collaborative activities

TB/HIV activities continue to make impressive progress – the number (%) of TB patients whose HIV status was ascertained continues to increase and proportion of HIV-infected TB patients linked to ART is also showing an increasing trend with some states like Karnataka crossing 70%. Gujarat has made impressive progress in ascertaining HIV status of TB patients and for third quarter, 2011, more than 90% of registered TB patients knew their HIV status; mainly attributable to the scale-up of Facility integrated ICTCs (F-ICTCs) and their co-location at DMCs. Decentralizing and integrating HIV testing into the general health system is the key strategy planned in the next five years. Recent amendments in ART guidelines by NACO mean that now, all HIV-infected TB patients are to be initiated on ART, irrespective of CD4 count and type of TB. This is likely to ease out the operational hurdles involved in CD4 testing and improve the linkages to ART. The provision of travel support to HIV-infected TB patients using funds under NRHM additionalities would further improve linkages

to ART. CTD has amended the TB/HIV scheme so that the 10-bedded Community Care Centres (CCC) are now eligible to make use of this scheme. This initiative is expected to increase the uptake of TB/HIV NGO-PP schemes under RNTCP and will be carefully monitored. CTD and NACO have jointly decided to test the operational feasibility of provision of Isoniazid Preventive Therapy for PLHIV at ART centres; National Institute for Research in TB(formerly TRC) would be leading this study.

In India, the number of people with diabetes is estimated to increase in the coming years and, this can seriously threaten TB control in the country. Available evidence shows that people with diabetes mellitus have a significantly increased risk of active TB which is two to three times higher than people without diabetes. Recent data from Tamil Nadu and Kerala indicate a very high prevalence of DM among TB patients. In addition, evidence also shows that diabetes worsens TB treatment outcomes - increased death, failure and relapse rates. In this regard, a National Stakeholders meeting was organized on 11th and 12th October, 2011 at New Delhi. At the national stakeholders' meeting, it has been decided to test the feasibility of bi-directional screening (Screening TB patients for DM and DM patients for TB) within routine health care services.

International AIDS Conference

XIX International AIDS Conference, convened by the International AIDS Society (IAS) and international, regional and local partners will be held in Washington D.C., U.S. from 22 to 27 July 2012.

For more information, visit www.aids2012.org

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SIXTY SIXTH NATIONAL CONFERENCE ON TUBERCULOSIS AND CHEST DISEASES: A BRIEF REVIEW

K.K. Chopra*

The 66th National Conference on Tuberculosis and Chest Diseases (NATCON 2011) was organized by the Uttrakhand State Tuberculosis Association (UKTBA) under the auspices of the Tuberculosis Association of India (TAI) from 18th to 20th November, 2011. The venue of the Conference was AMN Ghosh Auditorium, ONGC, Kolagarh Road, Dehradun. Dr. Rajesh Naithani, Organizing Secretary and his team worked hard to make the conference a grand success. The team worked under the overall advice and guidance of Dr. D. Behera, President of the Conference and Dr. Rohit Sarin, Vice Chairman of Tuberculosis Association of India. Over 300 delegates attended the Conference.

The conference was inaugurated by the Hon'ble Minister of Parliamentary Affairs, Government of India, Shri Harish Rawat. The Minister also released the souvenir brought out on the occasion. Dr. Rohit Sarin, Vice-Chairman, TAI, welcomed the delegates and explained the activities to be undertaken during the conference.

Dr. D.Behera, President of the conference, delivered the presidential address. Dr. Behera described the journey of TB control and lung health through recent years. He highlighted the recent developments of RNTCP implementation, TB-HIV Co-infection, TB and Tobacco association, TB and diabetes, impact of air pollution on lung health and he continued his discussion through lung cancer and latest developments in its management.

Key note address was read by Dr. G.R. Khatri (President, World Lung Foundation of South East Asia) in the absence of Chairman, TAI, Dr. R.K. Srivastava, who could not attend the Conference because of his pre-occupation. Dr.Khatri highlighted the problem of tobacco usage in Uttrakhand state and the project on smoke free being conducted in the state. He congratulated the Tuberculosis Association of India (TAI) on organizing this biggest event and highlighted its role, as an NGO, in supplementing and complementing the efforts of the government.

Dr. S.P. Agarwal, President of Tuberculosis Association of India, in his key-note address focused on challenges of tuberculosis in urban settings. He said "the burden of suffering and economic loss caused by TB is an affront to our conscience. TB is a curable and preventable disease. TB continues to be a public health problem in the world despite the availability of highly effective treatment regimens. HIV and TB form a lethal combination, each speeding the other's progress. TB-HIV co-infection and drug resistant tuberculosis aggravate the TB situation globally. TB is a leading cause of death in HIV infected persons and HIV infection is the most potent risk factor for developing active TB disease from a latent TB infection."

Dr. V.K. Arora, Hony. Technical Adviser of TB Association of India, also addressed the gathering and highlighted the activities of TAI and its State Associations.

Dr. Naithani, Organising Secretary of the conference read out the citations for various awards of TAI which were presented to the recipients by the Union Minister. The inaugural function ended with a vote of thanks by Smt. Poonam Kimothi, Honorary Secretary, Uttrakhand TB Association.

The Scientific Programme Committee of the Conference had chalked out a very useful programme. On the morning of 18th November, a CME programme was held for the post graduate students and young delegates. Eminent speakers gave lectures on different aspects of Tuberculosis.

* Director-Incharge, New Delhi TB Centre

During the main conference, besides three prestigious orations, one guest lecture, seven symposia and one RNTCP plenary session, there were 60 oral paper presentations and 60 poster presentations. Dr. P.K. Sen TAI Gold Medal Oration was delivered by Dr.D. Behera, Director, LRS Institute of TB and Respiratory Diseases on the subject of "TB Control to total lung health care". Lupin-TAI Oration was delivered by Drs. S.N. Rai and Tasleen Syed on the subject of "PPM in DOTS". Dr. S.N. Tripathy Memorial Oration was delivered by Dr. Rakesh Dayal on the subject of "Programmatic Management of Drug Resistant TB – Experience in Tribal and Geopolitical settings of Jharkhand". The OA Sarma guest lecture was delivered by Dr. Vijay Chhajlani on the subject of 'RNTCP – Madhya Pradesh: Strategy, Status, Initiatives and Vision".

RNTCP session was coordinated by Programme Manager of RNTCP in India and DDG (TB) Dr. Ashok Kumar. He introduced the latest developments of programme and also explained his future vision about the programme. Six speakers during the session deliberated on 'Priorities of RNTCP focusing on DOTS', 'Prevention and Management of MDR TB', 'TB and HIV Control Programme', 'Trained Manpower Development challenges under RNTCP', 'Monitoring and Supervision Challenges' and 'ACSM and PPM Challenges'. The session generated lot of fruitful discussion among speakers and delegates. Dr. Ashok Kumar assured the audience about their concerns for the programme and implementation of their suggestions.

Session sponsored by the Union highlighted the partnerships in the programme in the form of two lectures, namely; 'Reaching the Unreached – Role of ACSM' and 'Experiences from project Axshya'. Session conducted by FIND on "Partnerships in TB Diagnostics" included deliberation on recent advances in TB Diagnostics, Medical Colleges' involvement in LED Project, Lab Upgradation for recent diagnostics and Molecular Diagnostics.

The meeting of the Standing Technical Committee was held on 19th November, 2011 in which next venue of the conference was discussed in addition to other discussions. The meeting of the State Secretaries was held on 20th November, 2011.

A colourful exhibition was the highlight of the conference. Different organisations, including TAI and IUATLD, had put up informative stalls giving useful information on TB and chest diseases through charts and working models. A number of informative literature, brochures and books were distributed among visitors.

NATCON 2011 held in Dehradun was an excellent package of academic and social feast. The hospitality offered by the Organizing Committee was superb and the delicious food picked from the various areas of Uttrakhand were the highlights of the various meals wherein different menu was served on different days.

In the Business and Concluding Session, Dr. V.K.Arora, Honorary Technical Adviser, gave a brief resume of the Conference activities from the start till the conclusion of the Conference wherein it was highlighted that all the sessions were well attended and the younger workers were participating in large numbers.

Under Rule 3 (xiii) of the Rules and Regulations of TAI, Drs. K.K. Chopra, Jai Kishan, Prem Kumar and L.S. Chauhan were elected as representatives of the National Conference to serve on the Central Committee.

Dr. Rohit Sarin proposed a vote of thanks on behalf of the delegates and Dr. Naithani on behalf of the Organising Committee.

Short Communication

MYCOBACTERIUM TUBERCULOSIS TRIGGERS AUTOIMMUNITY ?

Vandana Pradhan, Manisha Patwardhan , Amita Athavale *, Syted Taushid * and Kanjksha Ghosh

(Received on 7.7.2011; Accepted after revision on 28.12.2011)

***Summary*:** Mycobacterial infections are known to induce the development of autoantibodies. This study was therefore carried out in endemic areas to look for the prevalence of autoantibodies in pulmonary and extra pulmonary tuberculosis, with and without rheumatological symptoms suggesting a possible role of mycobacterial infection triggering autoimmunity. The results reveal that there is a need for further studies to be carried out in relation to possible autoimmune phenomenon linked with *Mycobacterium tuberculosis* infections. Tuberculosis patients should ideally be screened for the presence of various autoantibodies, particularly for a detailed study on anti-nuclear antibody (ANA) specificities. Their significance has to be deciphered to understand the role of these background autoantibodies produced. It is important to screen all tuberculosis patients for autoantibody profile and should be followed up after the treatment for any flaring up of autoimmune related symptoms. **[*Indian J Tuberc 2012; 59:* 49 - 51]**

***Key words*:** Tuberculosis, Infection, Autoimmunity, Autoantibodies

INTRODUCTION

Autoimmune diseases are a leading cause of morbidity and mortality, with a growing mass of evidence implicating infections. The autoimmune diaseses result from inappropriate responses of the immune system to self antigens. The etiology of autoimmune disease remains largely unknown but candidate etiological factors include genetic abnormalities and infection.[2] Populations with exposure and consequent resistance to tuberculosis show increased frequency of autoimmune diseases, while populations which have not been exposed to tuberculosis have a low incidence of autoimmune disease.[3] Mumbai is an endemic area for tuberculosis and a high prevalence of tuberculosis is due to the low socioeconomic levels and poverty.[4] This study was carried out to look for the prevalence of autoantibodies in pulmonary and extra pulmonary tuberculosis with and without rheumatological symptoms. The patients who were suffering from tuberculosis had significantly high titres of autoantibodies like anti-nuclear antibodies (ANA) and anti-neutrophil cytoplasmic antibodies (ANCA) in them.

This prospective study was conducted on 120 subjects over a period of 18 months (2008-2009). This included 30 clinically diagnosed cases of tuberculosis without rheumatological symptoms, pulmonary (PTB) or extra pulmonary and 30 cases of tuberculosis with rheumatological symptoms like joint pain, myalgia, arthritis, arthralgia, back pain, rashes, etc. A disease control group included 30 patients having rheumatological manifestations without clinical presentation of tuberculosis and remaining 30 were normal healthy individuals. These patients were tested for various autoantibodies like anti-nuclear antibodies (ANA), anti-double stranded antibodies (anti-dsDNA), anti-neutrophil cytoplasmic antibodies (ANCA) and anti-histone antibodies (AHA) using commercially available Indirect Immunofluorescence (IIF) kits, BioRad, USA and Euroimmune, Lubeck. It was observed that 7/30 (23.3%) Tuberculosis patients with rheumatological symptoms showed the presence of autoantibodies with a significantly high titres value ($p< 0.004$), of which ANA positivity was the highest (22.7%). Four out of 30 (13.3%) tuberculosis patients without rheumatological symptoms also had autoantibodies ($p<0.05$), of which 33 % had lymph node tuberculosis. When further tested for ANA specificities, none of them had AHA, suggesting that

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the autoantibody development is not due to the standard anti-tuberculosis drug treatment leading to a possible autoimmune phenomenon in them. On specific ANA-BLOT testing (Euroimmune, Lubeck) for all ANA positive sera, it was observed anti-Ro antibodies were more common in tuberculosis patients with rheumatologic symptoms. Anti-Ro antibodies are also called as the anti-SS-A antibodies which are produced against ribonucleoprotein (nRNP) antigen and are found to be present in about 30-50% of Systemic Lupus Erythematosus (SLE) patients and 70-90% patients of Sjogren's syndrome.

Thus in India, M*ycobacterium tuberculosis* infection may trigger autoimmune response but patients may or may not present with rheumatological symptoms, like joint pain, myalgia, arthritis, arthralgia, back pain, rashes etc. These patients need to be evaluated for the presence of various autoantibodies in them. The Role of infections in triggering autoimmunity has been known since long and is linked mainly with following two mechanisms: 1) Up regulation of co stimulators on antigen presenting cells which present the self antigen to the T cells, resulting in breakdown of clonal anergy and 2) Molecular mimicry – in which microbes may express antigens that have the same amino acid sequence as self antigen. This may result in activation of self reactive T cells. There are also some Indian reports suggesting the role of *Mycobacterium tuberculosis* infection precipitating SLE in patient from endemic areas. Ghosh et al, 2009 had reported that 14 patients with SLE out of 70, had antecedent tuberculosis. A spectrum of anti-neutrophil cytoplasmic antibodies (ANCA) in patients with pulmonary tuberculosis has also been reported. [5,6]

Mycobacterial infections are also known to induce autoantibodies, some of which are known to be diagnostic markers for some autoimmune diseases, and there is a doubt that these autoantibodies may play a role in the pathogenesis of autoimmune disorders like ANCA associated vasculitis (AAV).[4] In TB cases, among the ANCA positives, 47.6% had anti-Myeloperoxidase (anti–MPO) antibodies and 28.6% had anti-Proteinase (anti–PR3) antibodies. The latter cases along with pulmonary and renal manifestations could be diagnosed as Wegener's Granulomatosis (WG) cases which are often mistaken and also misdiagnosed to be TB cases, but do not respond to standard AKT treatment. [6,7] It is observed that perinuclear immunofluorescence pattern with corresponding anti-MPO antibodies is commonly encountered in TB cases, but there is also a small group of patients having WG, either in its limited or classical form. In such cases the detection of ANCA with cytoplasmic immunofluorescence pattern and presence of anti-PR3 antibodies, would surely help in early and proper diagnosis. Such cases create a doubt whether they are true TB cases or WG cases and need to be thoroughly evaluated clinically and histopathologically with careful monitoring of their response to treatment.[8]

Further as there are many clinical similarities between TB and WG, a positive ANCA test in patients living in countries with a high prevalence of TB must be carefully interpreted as indicative of systemic vasculitis, especially when no signs of extra pulmonary involvement are seen.[9] In a group of TB patients having renal involvement, a higher incidence of anti-nuclear antibodies (ANA) was noted while incidence of ANCA was low.[4] In TB cases, raised ANA and ANCA levels have been noted among patients receiving Isoniazid treatment and ANA positivity was further found to correlate well with the duration of treatment. Isoniazid can be transformed by MPO into active metabolites with the development of cytotoxic products which could generate neutrophil damage with subsequent production of ANCA. Mycobacterial infections might be associated with exposure of immune system to slightly denatured or sequestered autologous tissue antigens, therefore autoantibodies raised against mycobacterial antigens may lead to an autoimmune condition in susceptible individuals. The presence of autoreactive antibodies in tropical infections may also result from polyclonal B cell activation or stimulation of autoantibodies to certain cross reactive

microbial antigens that may have been modified by host environment. ANCA in infections probably may indicate a secondary immune response, indicating neutrophil activation.

Hence there is a need for some further studies to be carried out related to possible autoimmune phenomenon linked with *Mycobacterium tuberculosis* infections in endemic areas where tuberculosis patients should ideally be screened for the presence of various autoantibodies, particularly for a detailed study on ANA specificities and its significance has to be deciphered to understand the role of these background autoantibodies produced. Tuberculosis patients should be followed up after the treatment for any flaring up of autoimmune related symptoms. Also the cause of possibly related autoimmune phenomenon should be stressed upon, so that the most susceptible gene/genes can be discovered and that can be targeted for immunotherapeutic treatment for tuberculosis leading to development of newer modalities.

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FORUM

TUBERCULOUS EPIDIDYMITIS - CYTOLOGY - BASED DIAGNOSIS

We wish to share with you our experience where once again it is proved that confirmatory diagnosis of tubercular epididymitis can be the cytological one.

Significant role of FNAC in the diagnosis of chronic epididymal lesion has already been documented in the literature.[1,2]

Genitourinary tuberculosis is the second most common form of extra pulmonary tuberculosis.[3] Up to 20% of the patients with pulmonary TB have genitourinary lesions.[4]

This case is of twenty-two-year-old-male who was referred by the clinicians for hard nodular swelling in epididymis present since last three years.

Before undergoing FNAC, patient had USG done which showed bilateral hydrocoele and grade I Varicocoele.

On preliminary examination for cytological aspiration, we noticed palpable 1cmx1cm hard, fixed and non-tender nodule in head of epididymis. Overlying skin was normal. Patient gave no history of fever or any past illness.

Patient was subjected to FNAC, smears of which showed a few epithelioid macrophages scattered amongst necrotic background (Figure-1). Smears also showed abundant caseating necrotic material at places (Figure-2). There was no evidence of any abnormal cells in the smear.

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In view of absence of any significant past history (not disclosed by the patient), cytological diagnosis of granulomatous epididymitis was made. However when patient had turned up to collect the report, he was requested to give more details about past history , he then mentioned about past history of pulmonary tuberculosis five years back for which treatment was taken for six months.

Patient was reassured and was referred back to the clinicians for review regarding anti-TB treatment and further management.

Thus, tuberculosis may involve pulmonary and extra pulmonary locations[4] and we conclude by mentioning that FNAC is a valuable tool in the diagnosis of epididymal nodular lesion. Even in the absence of any past clinical details, it can lead us to the confirmatory diagnosis of tuberculous epididymitis so that further procedures such as biopsy can be avoided.

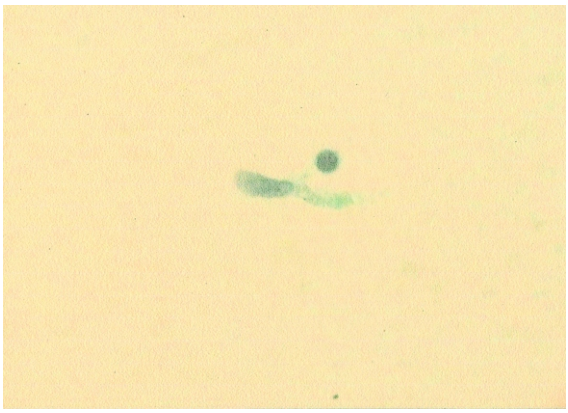

Figure 1: Smear (pap) showing typical epithelioid histiocyte against necrotic background

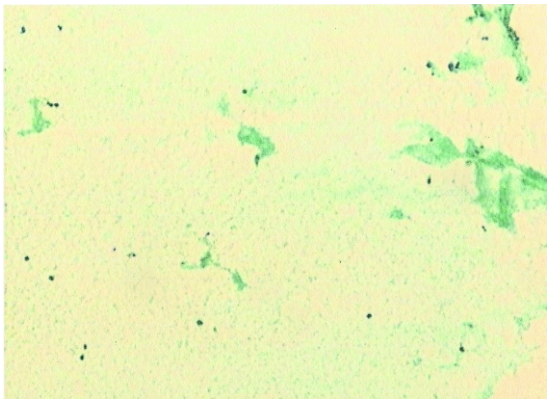

Figure 2: Smear (pap stained) showing caseous necrotic material and scattered lymphocytes.

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GUIDELINES FOR CONTRIBUTORS

GENERAL

The *Indian Journal of Tuberculosis (IJT)* is published four times in a year; January, April, July and October. It publishes original articles on tuberculosis, respiratory diseases, case reports, review articles, and abstracts of articles published in other medical journals and book reviews. Every issue contains editorial sections on contemporary subjects, radiology forum and a forum for readers to express their opinions on published articles and raise questions on subjects appearing in the journal.

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All correspondence relating to the *IJT* should be addressed to: *The Editor, Indian Journal of Tuberculosis,* Tuberculosis Association of India, 3 Red Cross Road, New Delhi - 110 001.

Articles are published on the understanding that every author confirms his participation in the study concerned and approves its content, and an affirmation that the article is original and has not been published/submitted for publication elsewhere and will not be so submitted, if accepted for publication in the *IJT.* A letter to this effect signed by the author should accompany the article.

All received articles are published, if found suitable, after completion of basic formalities. Notification of acceptance or rejection will be sent within three months of receipt. The decision of the Editor is final who reserves the right to make editorial corrections.

PREPARATION OF MANUSCRIPTS

Manuscripts should conform to the Uniform Requirements for Manuscripts submitted to the Biomedical Journals (for further details see Ann Intern Med 1997; 126: 36-47). Articles on clinical research should conform to the standards defined in the Helsinki Declaration.

Three copies of the manuscripts, including diagrams and photographs, typed on one side of the page with double spacing and wide margins should be submitted. To facilitate referral, it would be appreciated if compact diskettes are also enclosed. The preferred package is MS Word. The author should mention e-mail address, telephone and fax numbers apart from complete postal address with PIN code. Articles can also be sent by e-mail at tbassnindia@yahoo.co.in.

All submitted manuscripts should have a definite format comprising the following sections: Title page, Summary, Introduction, Material and Methods, Results, Discussion, Acknowledgements and References.

Title page

This should contain: (1) A concise informative title; (2) The name of the principa1 author followed by names of other authors without giving qualification or position held, except numera1 on top of last letter of name; (3) A running title usually not exceeding five words; (4) A word count of the text, excluding references, tables and figures; (5) In the case of original articles, a few key words for indexing purposes, using where possible, terms of medical subjects headings list from index medicus. The position held by each author in any institution should be indicated at the bottom of the title page along with the name and address of the author to whom correspondence regarding the manuscript has to be sent. Fax and telephone numbers (both landline and mobile) and e-mail ID should also be given.

Summary

An informative summary of not more than 250 words should be provided that can be understood without reference to the text (see Ann Intern Med 1990; 113: 69-76). The summary should be as per Vancouver format as follows: Background, Aims, Methods, Results and Conclusions. Unstructured

summaries may be submitted for review articles, case reports and short communications (100 words).

Text

Heading should conform to the text of the article. Normally only two categories of heading are used. Major headings shou1d be in capital letters and minor in upper lower case letters at the left-hand margin. The sub-titles should not be numbered in figures or alphabetically

The text should be written as lucidly as possible.

Numerals should be spelt out from one to nine (except measurement) and when beginning a sentence.

l. Research and experimental manuscripts should follow the usual conventions, as fo11ows:

Introduction: Setting forth clearly the aim of the study or the main hypothesis, with reference to previous studies and indicating the method used.
Material and Methods: used in the study.
Results: Presented in logical sequence in the text, with tables and illustrations. All the results of the tables should not be repeated in the text; only important results should be emphasized.
Discussion should be related to the aims, objects and results of the study.

Care should be taken that language is grammatically correct and fluent, that all relevant information is included, irrelevant details omitted and repetitions, especially from section to section, avoided.

In case reports, the sections on *"Material and Methods"* and *"Results"* are replaced by the section *"Clinical Record',* and all other sections are appropriately shortened.

2. Other papers can be sub-divided, as the authors desire: the use of headings enhances readability.

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References cited in the text and given at the end of the manuscript should conform to the Vancouver style. The authenticity of the references is the responsibility of the author. They must be numbered in the order in which they are cited in the text, and should be numbered in Arabic numerals in superscript. References that are cited more than once should retain the same number for each citation. The truly scientifically acceptable references are those of publications that can be consulted. Permission from the source(s) of information for citing their work must be obtained beforehand. All the numbered references in the text should be typed out in detail at the end of the manuscript, in the same numerical order as they appear in the text.

Journal: References to an article in a periodical should include the authors' names (list all authors when six or fewer, when there are more, list only the first three authors and add "et al"), the full title of the article, the name of the cited journal in its usual abbreviated form according to the *Index Medicus,* year of publication, tome or volume number, first and last page numbers in full:

e.g. Jain NK, Chopra KK, Prasad G. Initial and Acquired drug resistance to Isoniazid and Rifampicin and its implications for treatment. *Indian J Tuberc* 2002; **39**: 121-124.

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Chapter in a book: Reference to a chapter in a book should include the authors' names, the title of the chapter with the word "In" preceding the reference of the work:

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RS, Muller NL, Colman N, Pare PD, Bralow L, ed Fraser and Pare's *Diagnosis of Diseases of Chest;* 4th Ed; Vol III. Philadephia: W.B. Saunders Co, 1999: pp 2021-2048.

Reference to electronic material: If references are made to electronically published material, as much of the information as for other reference sources should be provided, the html address and the date last accessed.

Personal communication: References to personal communications should be given in the text with the name of the individual cited and with his/her consent.

Acknowledgements

Acknowledgements should be brief (not more than six lines). Acknowledge only those persons who made substantial contribution to the study and all sources of support in the form of grants.

Tables

Tables should be referred to consecutively in the text, placed after the list of references on separate sheets of paper, and should be numbered in Arabic numerals which are used for reference in the text. A short descriptive title should appear above the table, each column should have a short or abbreviated title. All abbreviations and necessary explanatory notes should be given below the table. The number of tables should be kept to a basic minimum to explain the most significant results.

Figures

Figures should be referred to consecutively in the text, placed after the list of references on separate sheets of paper, and should be numbered in Arabic numerals which are used for reference in the text. A short descriptive title should appear above the figure. Figures can be inserted into the word document for submission or uploaded separately as image files (.jpg, .gif, or .tif). If this is not possible, good quality (camera ready) prints of the figures must be provided.

Line drawings (curves, diagrams, histograms) should be provided in black and white. For optimal clarity, avoid shading.

Half-tone figures should be clear and highly contrasted in black and white. Photo- micrographs should have internal scale where appropriate. X-ray films should be careful1y made to bring out the details to be illustrated with an overlay indicating the area of importance.

Illustration: Legends for photographs should be typed separately with appropriate indication regarding the photograph to which a legend pertains. Photographs (black and white prints) should be clear, glossy and unmounted. Facilities for printing photographs in four colours as illustrations in case reports are available. Contributors are requested to preferably send colour photographs of their clinical material. Each photograph should carry, on its reverse, the title of the paper, and an arrow indicating the top edge of the photograph in pencil. It should be put in an envelope and properly labelled on the outside and attached to the article.

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conform to recognized scientific use i.e. SI units.

LENGTH OF TEXT

Editorial text can be up to 500 words with five references

Review articles are from those especially requested persons, who have acknowledged competence in given subjects. Text can be up to 4500 words, a structured or unstructured summary of maximum 250 words, 10 tables/figures and 50 references. **Leading articles** are by those who have expertise in selected aspect of a subject.

Original articles deal with planned studies that have been duly completed and convey definite conclusions from the data presented in the text. Text can be up to 2500 words, a structured summary of maximum 250 words, seven tables/figures and 35 references. Preliminary communications from research still in progress could be submitted exceptionally, if the topic is important and the interim results could be of interest.

Short communications can be of a text up to 1000 words, a summary of 100 words, two tables/figures and 10 references.

Case reports present problems of unusual clinical interest which have been systematically and fully investigated and where a firm diagnosis has been established with reasonable certainty, or the result of therapeutic management is of significance. Text can be up to 1000 words, a summary of 100 words, two tables/ figures and 10 references.

Workers in the field of Tuberculosis and Respiratory Diseases are invited to contribute to the **Radiology Forum** by submitting brief reports of patients with interesting clinical and radiological features for publication. These will be published, provided that:

(a) the condition is of clinical and radiological interest;
(b) photographs (10 cm x 8 cm) are of suitable quality for printing;
(c) the diagnosis in each case has been confirmed;
(d) the chest radiograph is accompanied by brief clinical account, not exceeding 500 words, and five references

Forum, in the form of letters to the Editor, provides a platform to readers for expressing their opinions and is a channel of communication with the journal and its readers. It could be used for making suggestions, scientific critique on published articles or for reaching independent conclusions, for asking questions on subjects covered by the journal and for providing supplementary information, either confirming or contradicting the conclusions reached in the article. Such letters can be up to a text of 1000 words with two tables/figures and 10 references. Only the most important agreements, disagreements/suggestions may be chosen for commenting. It is usual to send a copy of such letters to the authors for obtaining a response, if any, after editorial changes. The response, similarly, has to be brief and relevant.

Correspondence can be up to 500 words without tables or figures and five references.

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The journal is available online on our website www.tbassnindia.org.

ABSTRACTS

Usefulness of Tumor Marker CA-125 Serum Levels for the Follow-Up of Therapeutic Responses in Tuberculosis Patients with and without Serositis

Wei-Chang Huang, Chih-Wei Tseng, Kai-Ming Chang, Jeng-Yuan Hsu, Jiann-Hwa Chen and Gwan-Han Shen. *Jpn J Infect Dis* 2011; **64**: 367-72.

The aim of this study was to determine the usefulness of cancer antigen 125 (CA-125) se- rum levels in patients with tuberculosis (TB) with and without tuberculous serositis. A total of 64 TB patients with a mean age of 58.17± 19.05 years were enrolled in this observational case series study. All patients underwent blood sampling for the measurement of CA-125 serum levels before treatment. If the CA-125 serum levels were found to be elevated, the patients underwent blood sampling in the initial treatment phase, continuation treatment phase, and every six months thereafter for two years. The treatment outcomes of the pulmonary TB group were evaluated using chest radiography and sputum examinations, and those of the tuberculous serositis group were evaluated on the basis of the amounts of fluid determined by ultrasound. All patients in the tuberculous serositis group and 45% of the patients in the pulmonary TB group had elevated CA-125 serum levels before treatment. The pretreatment mean CA-125 serum level was significantly higher in the tuberculous serositis group than in the pulmonary TB group. CA-125 serum levels decreased along with improvement in anti-TB treatment outcomes in both the groups. In conclusion, the CA-125 serum levels in combination with clinical responses, chest radiography, and sputum examinations, can offer better monitoring of therapeutic responses in anti-TB treatment.

ãä T cells response to *Mycobacterium tuberculosis* in pulmonary tuberculosis patients using preponderant complementary determinant region 3 sequence

Xueyan Xi, Xiqin Han, Liang Li and Zhendong Zhao. *Indian J Med Res* 2011; **134**: 356-61.

The unique immunological functions of ãä T lymphocytes to contribute immunity against *Mycobacterium tuberculosis* attracted interest of researchers. However, little is known about the specificity of ãä T cell in tuberculosis patients and the lack of exact tuberculosis antigen recognized by ãä T cells limited its application. The analysis of complementary determinant region (CDR)3 sequence characteristic in ãä T cells of tuberculosis patients would contribute to understand the distribution specificity of ãä T cell. In present study, we investigated the diversity of the ã9/ä2 T cell immunorepertoire and analysed the specificity of the expressed CDR3 in pulmonary tuberculosis patients. The total RNA in peripheral blood mononuclear cell of 50 pulmonary tuberculosis patients and 10 healthy controls was extracted. The polymerase chain reaction was used to specifically amplify the CDR3 region of ã9 and ä2 chain. The PCR products were ligated into the pGEM-T easy vector. The plasmid DNA was sequenced using the ABI3700 and the T7 primer. Our findings showed that predominant CDR3 sequence of ä2 chain in pulmonary tuberculosis patients was CACDTLVSTDKLIFGKG. The sequence specifically exists in almost all pulmonary tuberculosis patients. The conserved hydrophobic acid residue in 97 positions is present in the ãä T cell reactive to *M. tuberculosis.* The length of ä2 CDR3 in pulmonary tuberculosis patients has no relation with the disease progress. Our results suggest that ãä T cells appear to use CDR3 sequence to recognise *M. tuberculosis* antigen. ãä T cells reactive to *M. tuberculosis* were diverse and polyclonal.

Improving tuberculosis contact tracing: the role of evaluations in the home and workplace

R. Duarte, M. Neto, A. Carvalho and H. Barros. *The International Journal of Tuberculosis and Lung Disease* 2012; **16**: 55-60.

In 2004, the tuberculosis (TB) contact screening strategy in Vila Nova de Gaia, Portugal, was changed from targeting only close contacts identified by interviews with the index patient (reflecting national

policy) to include visits to the patient's home and workplace. The objectives of the study were to find out 1) whether the new strategy increased adherence to TB screening procedures, 2) whether the strategy identified more at-risk contacts and 3) whether the strategy increased prevention of TB. We compared TB contact tracing during the periods 2001-2003 and 2004-2006. The numbers of identified and screened contacts and the results of screening procedures (number of patients with active TB and latent TB infection [LTBI] detected per index case) were analysed. The number of instances of active TB prevented and the numbers of contacts that had to be screened to prevent one such instance were calculated and compared for both screening strategies. Home and workplace visits helped to identify more at-risk contacts (8.4 per index patient) than interview (2.5 per index patient), and improved adherence (87.3% of identified contacts were screened compared to 67.6% previously). More patients with active TB and LTBI were detected (1.4 per index patient compared with 0.75 per index patient previously), and more TB cases were prevented. The newly implemented contact screening programme, featuring home and workplace evaluation of TB patient contacts, improved adherence to screening procedures, identified more at-risk contacts should prevent more TB cases in the future.

Evaluation of the GenoType® MTBDR*sl* assay for susceptibility testing of second-line anti-tuberculosis drugs

H. M. Said, M. M. Kock, N. A. Ismail, K. Baba, S. V. Omar, A. G. Osman, A. A. Hoosen and M. M. Ehlers. *The International Journal of Tuberculosis and Lung Disease* 2012; **16**: 104-10.

The GenoType ® MTBDR*s/*assay is a new rapid assay for the detection of resistance to second-line anti-tuberculosis drugs. The objectives of the study were to evaluate the MTBDR*s/*assay on 342 multidrug-resistant tuberculosis isolates for resistance to ofloxacin (OFX), kanamycin (KM), capreomycin (CPM) and ethambutol (EMB), to compare the results to the agar proportion method, and to test discrepant results using DNA sequencing. The sensitivity and specificity of the MTBDR*s/*assay were respectively 70.3% and 97.7% for OFX, 25.0% and 98.7% for KM, 21.2% and 98.7% for CPM and 56.3% and 56.0% for EMB. DNA sequencing identified mutations that were not detected by the MTBDR*s/*assay. The 8/11 phenotypically OFX-resistant isolates had mutations in *gyr* A (2/8 had an additional mutation in the *gyr* B gene), 1/11 had mutations only in the *gyr* B gene, 6/21 phenotypically KM-resistant isolates had mutations in the *rrs* gene, and 7/26 and 20/26 pheno- typically CPM-resistant isolates had mutations in the *rrs* and *tly* A genes. The MTBDR*s/*assay showed lower sensitivity than previous studies. The assay performed favourably for OFX; however, it was less sensitive in the detection of KM/CPM resistance and demonstrated low sensitivity and specificity for EMB resistance. It is recommended that the MTBDR*s/*assay include additional genes to achieve better sensitivity for all the drugs tested.

Prevalence of asthma and associated factors among schoolchildren in rural South India

B. B. Dhabadi, A. Athavale, A. Meundi, R. Rekha, M. Suruliraman, A. Shreeranga and S. Gururaj. *The International Journal of Tuberculosis and Lung Disease* 2012; **16**: 120-26.

The objectives of the study were 1) to estimate the prevalence of asthma among secondary school children in a rural area in Karnataka, South India, and 2) to identify risk factors associated with asthma among asthma patients. A cross-sectional study was undertaken among 588 secondary school children in a rural area in South India. A locally adapted version of the questionnaire used in an asthma prevalence study in Iowa, USA, was administered. The prevalence of asthma in the study group was 4.9%. In a multivariate model, significant association was found with sex (male predominance) and exposure to dust in the house. Place of residence, farm dwelling, household pets (cats or dogs), smokers in the family, type of cooking fuel used and the use of firewood without chimneys did not show any significant association. In the present study, the prevalence of questionnaire-diagnosed asthma in the study group was 4.9%. Of the total number of schoolchildren with asthma, 17 (58.6%) were detected who had not been diagnosed previously. One third of the children with asthma had visited emergency departments in the last 12 months, indicative of poor

asthma control. Another third suffered limitation of activity at home and or at school, which could indicate poor quality of life.

Seasonality of tuberculosis in New York City, 1990-2007

Parrinello, C.M., Crossa A. and Harris, T.G. *The International Journal of Tuberculosis and Lung Disease* 2012; **16(1)**: 32-8.

Several non-US-based studies have found seasonal fluctuations in the incidence of tuberculosis (TB). The current study examined patterns of TB seasonality for New York City verified TB cases from January 1990 to December 2007. Autocorrelation functions and Fourier analysis were used to detect a cyclical pattern in monthly incidence rates. Analysis of variance was used to compare seasonal mean case proportions. A cyclical pattern was detected every 12 months. Of the 34 004 TB cases included, 21.9% were in the fall (September-November), 24.7% in winter (December- February), 27.3% in spring (March-May), and 26.1% in the summer (June-August). The proportion of cases was lowest in fall ($P < 0.0001$) and highest in the spring ($P < 0.0002$). Possible explanations for seasonal variations in TB incidence include lower vitamin D levels in winter, leading to immune suppression and subsequent reactivation of latent TB; indoor winter crowding, increasing the likelihood of TB transmission; and providers attributing TB symptoms to other respiratory illnesses in winter, resulting in a delay in TB diagnosis until spring. Understanding TB seasonality may help TB programmes better plan and allocate resources for TB control activities.

Intervention to increase detection of childhood tuberculosis in Bangladesh

Talukder K., Salim M.A.H., Jerin I., Sharmin F., Talukder M. Q-K., Marais B.J., Nandi P., Cooreman E. and Rahman M.A. *The International Journal of Tuberculosis and Lung Disease* 2012; **16(1)**: 70-76.

Despite a well-functioning adult tuberculosis (TB) control programme, children with TB remain grossly under-detected in Bangladesh. It is conservatively estimated that annually around 21 000 children with TB go undetected, due to an almost exclusive focus on sputum smear-positive TB and the absence of training or guidelines in paediatric TB. To double child TB detection by increasing general awareness and training of health care workers at microscopy centres supported by the Damien Foundation (DF) Bangladesh, a cluster-randomised trial was carried out with provision of child TB guidelines, training and logistics support to staff of 18 microscopy centres, while 18 non-adjacent microscopy centres continued their usual practice and served as controls. Paediatric data on TB suspect referral and case detection were collected at baseline and during the intervention at both control and intervention sites. Child TB case detection increased in both intervention and control microscopy centres, but the increase was three times the baseline in the intervention centres (from 3.8% to 12%) in comparison to less than double the baseline in the control centres (from 4.3% to 7%, $P = 0.001$). Simple guidelines and training on child TB case detection, together with basic logistics support, can be integrated into the existing National TB Control Programme and improve service delivery to children in TB-endemic areas.

Risk factors for mortality among MDR- and XDR-TB patients in a high HIV prevalence setting

Gandhi N.R., Andrews J.R., Brust J.C.M., Montreuil R., Weissman D., Heo M., Moll A.P., Friedland G.H. and Shah N.S. *The International Journal of Tuberculosis and Lung Disease* 2012; 16(1): 90-98.

Recent studies suggest that the prevalence of drug-resistant tuberculosis (TB) in sub-Saharan Africa may be rising. This is of concern, as human immunodeficiency virus (HIV) co-infection in multidrug-resistant (MDR) and extensively drug-resistant (XDR) TB has been associated with exceedingly high mortality rates. The aim of the study was to identify risk factors associated with mortality in MDR- and XDR-TB

patients co-infected with HIV in South Africa. It was a case-control study of patients who died of all causes within two years of diagnosis with MDR- or XDR-TB. Among 123 MDR-TB patients, 78 (63%) died following diagnosis. CD4 count ≤ 50 (HR 4.64, *P* = 0.01) and 51-200 cells/mm 3 (HR 4.17, *P* = 0.008) were the strongest independent risk factors for mortality. Among 139 XDR-TB patients, 111 (80%) died. CD4 count ≤ 50 cells/mm 3 (HR 4.46, *P* = 0.01) and resistance to all six drugs tested (HR 2.54, *P* = 0.04) were the principal risk factors. Use of antiretroviral therapy (ART) was protective (HR 0.34, *P* = 0.009). Mortality due to MDR- and XDR-TB was associated with greater degree of immunosuppression and drug resistance. Efforts to reduce mortality must focus on preventing the amplification of resistance by strengthening TB treatment programmes, as well as reducing the pool of immunosuppressed HIV-infected patients through aggressive HIV testing and ART initiation.

Integrated detection of multi- and extensively drug-resistant tuberculosis using the nitrate reductase assay

Ramos E., Fissette K., de Rijk P., Palomino J.C. and Martin, A. *The International Journal of Tuberculosis and Lung Disease* 2012; **16(1)**: 110-14.

It currently takes 2-3 months to obtain a diagnosis for multidrug-resistant (MDR-) and extensively drug-resistant tuberculosis (XDR-TB). We evaluated the rapid non-commercial nitrate reductase assay (NRA), which is capable of the simultaneous detection of MDR- and XDRTB, and compared the results with the proportion method (PM). The sensitivity was respectively 97%, 99%, 100% and 94.6% for rifampicin (RMP), isoniazid (INH), ofloxacin (OFX) and kanamycin (KM). The specificity was respectively 100%, 95%, 95.7% and 99% for RMP, INH, OFX and KM. The turnaround time for NRA was 10- 14 days, compared to 4-6 weeks for the PM. Our study showed that NRA provided sensitive and specific detection of resistance to first- and second-line drugs.

6-month versus 36-month isoniazid preventive treatment for tuberculosis in adults with HIV infection in Botswana: a randomised, double-blind, placebo-controlled trial

Taraz Samandari, Fefera B Agizew, Samba Nyirenda, Segabriel Tedla, Thabisa Sibanda, Nong Shang, Barudi Mosimaneotsile, Oaitse I Motsamai, Lorna Bozeman, Margarett K Davis, Elizabeth A Talbot, Themba L Moeti, Howard J Moffat, Peter H. Kilmarx, Kenneth G Castro and Chales D Wells. *The Lancet* 2011; **377**: 1588-98.

In accordance with WHO guidelines, people with HIV infection in Botswana receive daily isoniazid preventive therapy against tuberculosis without obtaining a tuberculin skin test, but duration of prophylaxis is restricted to six months. We aimed to assess effectiveness of extended isoniazid therapy. In our randomised, double-blind, placebo-controlled trial, we enrolled adults infected with HIV aged 18 years or older at government HIV-care clinics in Botswana. Exclusion criteria included current illness such as cough and an abnormal chest radiograph without antecedent tuberculosis or pneumonia. Eligible individuals were randomly allocated (1:1) to receive 6 months' open-label isoniazid followed by 30 months' masked placebo (control group) or 6 months' open-label isoniazid followed by 30 months' masked isoniazid (continued isoniazid group) on the basis of a computer-generated randomisation list with permuted blocks of ten at each clinic. Antiretroviral therapy was provided if participants had CD4-positive lymphocyte counts of fewer than 200 cells per ì L. We used Cox regression analysis and the log-rank test to compare incident tuberculosis in the groups. Cox regression models were used to estimate the effect of antiretroviral therapy.

The trial is registered at ClinicalTrials.gov, number NCT00164281. Between Nov 26, 2004, and July 3, 2009, we recorded 34 (3·4%) cases of incident tuberculosis in 989 participants allocated to the control group and 20 (2·0%) in 1006 allocated to the continued isoniazid group (incidence 1·26% per year *vs* 0·72%; hazard ratio

0·57, 95% CI 0·33—0·99, p=0·047). Tuberculosis incidence in those individuals receiving placebo escalated approximately 200 days after completion of open-label isoniazid. Participants who were tuberculin skin test positive (ie, ≥ 5 mm induration) at enrolment received a substantial benefit from continued isoniazid treatment (0·26, 0·09—0·80, p=0·02), whereas participants who were tuberculin skin test-negative received no significant benefit (0·75, 0·38-1·46, p=0·40). By study completion, 946 (47%) of 1995 participants had initiated antiretroviral therapy. Tuberculosis incidence was reduced by 50% in those receiving 360 days of antiretroviral therapy compared with participants receiving no antiretroviral therapy (adjusted hazard ratio 0·50, 95% CI 0·26-0·97). Severe adverse events and death were much the same in the control and continued isoniazid groups. In a tuberculosis-endemic setting, 36 months' isoniazid prophylaxis was more effective for prevention of tuberculosis than was 6-month prophylaxis in individuals with HIV infection, and chiefly benefited those who were tuberculin skin test positive.

New Regimens to prevent Tuberculosis in adults with HIV Infection

Neil A. Martinson, Grace L. Barnes, Lawrence H. Moulton, Reginah Msandiwa, Harry Hausler, Malathi Ram, James A. McIntyre, Glenda E. Gray, and Richard E. Chaisson. *The New England Journal of Medicine* 2011; **365**: 1.

Treatment of latent tuberculosis in patients infected with the human immunodeficiency virus (HIV) is efficacious, but few patients around the world receive such treatment. We evaluated three new regimens for latent tuberculosis that may be more potent and durable than standard isoniazid treatment. We randomly assigned South African adults with HIV infection and a positive tuberculin skin test who were not taking antiretroviral therapy to receive rifapentine (900 mg) plus isoniazid (900 mg) weekly for 12 weeks, rifampin (600 mg) plus isoniazid (900 mg) twice weekly for 12 weeks, isoniazid (300 mg) daily for up to six years (continuous isoniazid), or isoniazid (300 mg) daily for six months (control group). The primary end point was tuberculosis-free survival. The 1148 patients had a median age of 30 years and a median CD4 cell count of 484 per cubic millimeter. Incidence rates of active tuberculosis or death were 3.1 per 100 person-years in the rifapentine–isoniazid group, 2.9 per 100 person-years in the rifampin–isoniazid group, and 2.7 per 100 person-years in the continuou isoniazid group, as compared with 3.6 per 100 person-years in the control group (P>0.05 for all comparisons). Serious adverse reactions were more common in the continuous isoniazid group (18.4 per 100 person-years) than in the other treatment groups (8.7 to 15.4 per 100 person-years). Two of 58 isolates of *Mycobacterium tuberculosis* (3.4%) were found to have multidrug resistance. On the basis of the expected rates of tuberculosis in this population of HIV-infected adults, all secondary prophylactic regimens were effective. Neither a 3-month course of intermittent rifapentine or rifampin with isoniazid nor continuous isoniazid were superior to six months of isoniazid.

Primary Isoniazid Prophylaxis against Tuberculosis in HIV-exposed children

Shabir A. Madhi, Sharon Nachman, Avy Violari, Soyeon Kim, Mark F. Cotton, Raziya Bobat, Patrick Jean-Philippe, George McSherry and Charles Mitchell. *The New England Journal of Medicine* 2011; **365**: 1.

The dual epidemic of human immunodeficiency virus (HIV) and tuberculosis is a major cause of sickness and death in sub-Saharan Africa. We conducted a double-blind, randomized, placebo-controlled trial of pre-exposure isoniazid prophylaxis against tuberculosis in HIV-infected children and uninfected children exposed to HIV during the perinatal period. We randomly assigned 548 HIV-infected and 804 HIV-uninfected infants (91 to 120 days of age) to isoniazid (10 to 20 mg per kilogram of body weight per day) or matching placebo for 96 weeks. All patients received Bacille Calmette–Guerin (BCG) vaccination against tuberculosis within 30 days after birth. HIV-infected children had access to antiretroviral therapy. The primary outcome measures were tuberculosis disease and death in

HIV-infected children and latent tuberculosis infection, tuberculosis disease, and death in HIV-uninfected children within 96 to 108 weeks after randomization. Antiretroviral therapy was initiated in 98.9% of HIV-infected children during the study. Among HIV-infected children, protocol-defined tuberculosis or death occurred in 52 children (19.0%) in the isoniazid group and 53 (19.3%) in the placebo group (P = 0.93). Among HIV-uninfected children, there was no significant difference in the combined incidence of tuberculosis infection, tuberculosis disease, or death between the isoniazid group (39 children, 10%) and the placebo group (45 children, 11%; P = 0.44). The rate of tuberculosis was 121 cases per 1000 child-years (95% confidence interval [CI], 95 to 153) among HIV-infected children as compared with 41 per 1000 child-years (95% CI, 31 to 52) among HIV-uninfected children. There were no significant differences in clinical or severe laboratory toxic effects between treatment groups. Primary isoniazid prophylaxis did not improve tuberculosis-disease–free survival among HIV-infected children or tuberculosis-infection–free survival among HIV-uninfected children immunized with BCG vaccine. Despite access to antiretroviral therapy, the burden of tuberculosis remained high among HIV-infected children.

TB HEALTH VISITORS' COURSE

The Tuberculosis Association of India organizes a TB Health Visitors' Course of nine month duration at New Delhi Tuberculosis Centre, New Delhi every year. The course is a desired qualification for appointment of TB health workers and well accepted by various agencies working for prevention and cure of tuberculosis.

The course is imparted free of cost. However, the participants have to make their own boarding/ lodging arrangements at Delhi for the course duration. The course imparts both theoretical and practical training and broadly covers the following subjects:

1. Tuberculosis Control and Public Health Nursing.
2. Hygiene (including General Hygiene, Personal hygiene, Mental hygiene and School hygiene).
3. First Aid and Home Nursing.
4. Anatomy and Physiology.
5. Social Welfare and Domestic Science including Household Management, Record Keeping, Nutrition and Dietetics.
6. Health Education.

This year course is scheduled to commence from 1st July, 2012.The minimum qualification for admission to this course is 10 + 2 with Science (Biology group) and the maximum age is 28 years as on 1st July, 2012. Relaxation of age for candidates working in government institutions may however be considered by the Selection Committee. Mere eligibility would not be the only criterion for selection of the candidates nor would it be a binding condition for selection.

Application forms and other details of course can be downloaded from Tuberculosis Association of India's website: **www. tbassnindia.org**. The last date for receipt of application forms at our office is 30th Apri, 2012.

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