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Editorial

TACKLING EXTENSIVELY DRUG RESISTANT TUBERCULOSIS (XDR-TB)

[*Indian J Tuberc 2013; 60:* 67 - 70]

Tuberculosis remains a major cause of morbidity and mortality worldwide. The rise and spread of drug resistance is threatening global efforts of tuberculosis control. Extensively drug-resistant tuberculosis (XDR-TB) is a severe form of drug-resistant TB, defined as tuberculosis caused by a *Mycobacterium tuberculosis* strain that is resistant to isoniazid and rifampicin among the first-line antitubercular drugs (multidrug-resistant tuberculosis; MDR-TB) in addition to resistance to any fluoroquinolone and at least one of the three injectable second-line drugs (SLDs), namely amikacin, kanamycin and/or capreomycin. The first reports of XDR-TB appeared in 2006.[1, 2] Since then, a total of 84 countries have reported cases of XDR-TB. The true scale of XDR-TB is unknown as many countries lack the necessary equipment and capacity to accurately diagnose it. An estimated number of 630,000 cases of MDR TB (460,000-790,000 out of ~12 million prevalent TB cases) were reported in the world in 2011 as per the 2012 WHO global tuberculosis report.[3] There were an estimated 310000 (range, 220 000–400 000) MDR-TB cases among notified TB patients with pulmonary TB in 2011. Almost 60% of these cases were in India, China and the Russian Federation. XDR-TB has been identified in 84 countries; the average proportion of MDR-TB cases with XDR-TB is 9.0% (6.7–11.2%). Levels of MDR-TB remain worryingly high in some parts of the world, notably countries in eastern Europe and central Asia. In several of these countries, 9–32% of new cases have MDR-TB and more than 50% of previously treated cases have MDR-TB.[3] By far, the largest number of cases of XDR-TB has been reported from South Africa (10.5% of all cases of MDR-TB in that country), owing to rapid spread among people infected with the human immunodeficiency virus.[4]

XDR-TB strains have arisen due to the mismanagement of individuals with MDR-TB. The global epidemic of drug-resistant tuberculosis is due to a combination of acquired resistance and primary transmission. Because XDR-TB is resistant to the most powerful first-line and second-line drugs, patients are left with treatment options that are much less effective and often have worse treatment outcomes. National programmes are failing to diagnose and treat MDR and XDR tuberculosis. Only 7% of estimated 440,000 cases of MDR-TB cases were reported to WHO and only a fifth were treated according to WHO recommended regimens.[3] A vast majority of the remaining cases probably are not diagnosed or, if diagnosed, are mismanaged. This problem remains despite the evidence that management of MDR and XDR tuberculosis is cost-effective.[5]

Within a year of the first reports of XDR-TB in 2006, isolated cases were reported in Italy that had resistance to all first-line anti-TB drugs and second-line anti-TB drugs that were tested.[6-8] In 2009, a cohort of 15 patients in Iran was reported who were resistant to all anti-TB drugs tested.[9] The terms ‘extremely drug resistant’ (XXDR-TB) and ‘totally drug-resistant TB’ (TDR-TB) were given by the authors reporting this group of patients. In 2012, Dr Udwadia reported four patients from Mumbai with TDR-TB[10], with subsequent media reports of a further eight cases which got lot of media publicity.[11] However, within a couple of weeks, the health authorities had rejected these claims, saying that all the cases were in fact XDR-TB infections. While the concept of TDR-TB is

easily understood in general terms, in practice, *in vitro* drug susceptibility testing (DST) is technically challenging and got limitations on its use. Conventional DST for the primary antitubercular drugs has been thoroughly studied and consensus reached on appropriate methods, critical drug concentrations that define resistance, and reliability and reproducibility of testing.[12] Reproducibility and reliability of DST for the SLDs are limited or have not been established. The correlation of DST results with clinical response to treatment has not yet been adequately established. Thus, a strain of TB with *in vitro* DST results showing resistance could, in fact, in the patient, be susceptible to these drugs. Lastly, new drugs are under development, and their effectiveness against these "totally drug resistant" strains has not yet been reported. For these reasons, the term "totally drug resistant" tuberculosis is not yet recognized by the WHO. For now, these cases are defined as XDR-TB, according to WHO definitions.[13]

Preventing initial infection with MDR and XDR tuberculosis and managing the treatment of existing cases appropriately are the keys to containing the spread of this disease. The discovery of patients with MDR or XDR-TB emphasizes the importance of ensuring that all care for tuberculosis, whether in the public or private sector, must conform to international standards in order to prevent the emergence of drug resistance.[14] Almost all countries must ensure appropriate diagnosis and treatment of cases of MDR-TB. National regulations for the quality and dispensing of anti-TB drugs, particularly of the second-line drugs, need to be strictly enforced. To achieve this, most countries require simultaneous scale-up of the diagnostic and treatment services for drug-resistant TB, and the provision of adequate and continuous supplies of quality-assured second line drugs for both MDR- and XDR-TB to meet the increased demand. XDR and TDR-TB raise many difficult issues concerning the management of patients, for example, whether to isolate patients, the need for institutional, palliative or end-of-life care, and the compassionate use of new drugs to prevent transmission of infection.[15]

Molecular diagnostics have made earlier and improved diagnosis of active disease possible. Laboratory expertise and resources are required for these tests to become available throughout the developing world. Globally in 2010, only 4% of new and 6% of previously treated TB patients were tested for susceptibility to isoniazid and rifampicin, while the Global Plan targets are 20% or more, and 100%, respectively. The number of reported cases of MDR-TB was only 18% of the estimated number of cases among TB patients notified in 2010.[15] And only around one quarter of them were treated in accordance with recommended international guidelines.

Tuberculosis control efforts are complicated by weak programmes with poor access to laboratory diagnosis and effective treatment. Investment in laboratory capacity and staff and the introduction of new rapid diagnostic tests are crucial. The World Health Organization (WHO) recommends that standard drug-susceptibility testing be performed at the same time that the Xpert MTB/RIF assay is performed to confirm rifampicin resistance and the susceptibility of the *M. tuberculosis* isolate to other drugs. Other screening tests for drug resistance include the microscopic-observation drug-susceptibility (MODS) assay, the nitrate reductase assay, and colorimetric reductase methods. The MODS assay simultaneously detects *M. tuberculosis* bacilli, on the basis of cording formation, and isoniazid and rifampicin resistance. Since most of these methods are not currently available in countries where tuberculosis is highly endemic, it is estimated that only 10% of cases of MDR-TB are currently diagnosed worldwide and only half of them receive appropriate treatment.[15] XDR-TB is extremely difficult to diagnose and treat in countries where the disease is endemic.

A review on 13 recent studies of XDR-TB show that XDR-TB can be successfully treated in up to 65% of patients, particularly those who are not co-infected with HIV. However, treatment

duration is longer and outcomes are, in general, poorer than for non-XDR TB patients. Early diagnosis and aggressive management of XDR-TB provide the best chance of positive outcome, but prevention is still paramount. Several new drugs belonging to new classes of anti-mycobacterial agents are under development, but until they are shown to be effective in properly conducted clinical trials, WHO cannot recommend their routine use.

Newer antituberculosis drugs offer the promise of shortened treatment regimens for drug-sensitive disease and more effective treatment for drug-resistant disease and latent infection. New vaccines against tuberculosis in advanced clinical trials offer hope for future tuberculosis control. Although these scientific developments are promising, the global economic crises continue to hinder tuberculosis control programmes. Strong political and financial commitments will be required to achieve global control of tuberculosis and avert millions of unnecessary deaths.

The WHO recommended Stop TB Strategy provides the framework for the effective large-scale treatment and control of both drug-susceptible and drug-resistant disease.[16] The Global Plan to Stop TB, 2011 – 2015, developed by the Stop TB Partnership, including WHO, estimates funding needs for implementation levels needed to achieve global targets.[17]

XDR-TB raises concerns of a future TB epidemic with restricted treatment options, and jeopardizes the major gains made in TB control. It is therefore vital that TB control be managed properly and new tools developed to prevent, treat and diagnose these patients. Preventing initial infection with MDR and XDR tuberculosis and managing the treatment of existing cases appropriately are the keys to containing the spread of this disease. Recent advances in diagnostics, drugs and vaccines and enhanced implementation of existing interventions have increased the prospects for improved clinical care and global tuberculosis control.

S. P. Rai*

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Original Article

OCCURRENCE OF NON-TUBERCULOUS MYCOBACTERIUM IN CLINICAL SAMPLES - A POTENTIAL PATHOGEN*

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Summary

***Background*:** Silent presence of non-tuberculous mycobacterium (NTM) has been observed since the last 100 years, but now the increasing incidence of NTM is of great concern for clinical microbiologists as well as clinicians. Although many advanced efforts are being made for identification and control of *Mycobacterium tuberculosis*, still the silently growing menace of non-tuberculous mycobacteria is receiving negligible attention.

Objectives: This study was aimed to find NTMs in positive cultures and identify them up to species level.

***Material & Methods*:** During the study period, i.e. from January 2009 to June 2011, a total of 4104 positive cultures were subjected to species identification by different morphological and biochemical tests. All the tests for identification were performed as per standard procedure along with the standard strains of NTM provided by JALMA, Agra.

***Results*:** The identification of positive cultures showed 4044/15581 (25.95%) *Mycobacterium tuberculosis* complex and 60/15581(0.38%) NTM. The mycobacterium species identification results showed that out of total 60 NTM, 21 different species of NTM were found and they belonged to all the four groups of runyon. The most common species identified in this study was *M.simiae* (07) followed by *M.avium*(06), *M.gordonae*(05), *M.kansasii*(05), *M.fortuitum*(05), *M.chelonae*(05), *M.pheli*(05), *M.terrae*(04), *M.szulgai*(02), *M.vaccae*(02), *M.flavescens*(02), *M. trivale*(02), *M.malmoense*(01), *M.scrofulaceum*(01), *M.intracellulare*(01), *M.xenopi*(01), *M.ulcerans*(01), *M.tusciae*(01), *M.triplex*(01), *M.septicum*(01), *M.mucogenicum*(01).

***Conclusion*:** The isolation of NTMs from different clinical samples indicated that they may be the causative agents for pulmonary and extra-pulmonary non-tuberculous diseases. Elaborate and focused studies are needed to differentiate NTMs amongst commensal/colonizer, pathogen and laboratory contaminants. **[*Indian J Tuberc 2013; 60:* 71 - 76]**

Key words: Non-Tuberculous mycobacterium, Lowenstein Jensen medium, *Mycobacterium avium*

INTRODUCTION

The reports of non-tuberculous mycobacterium (NTM) associated with pulmonary and extrapulmonary diseases are increasing every day. More than 125 species of NTM have been catalogued and available online out of which at least 42 species associate with disease in humans.[1] NTM was initially recognized as important only in 1982, when *Mycobacterium avium complex* (MAC) was isolated and considered as the most common opportunistic bacterial infection in AIDS patients. Thereon, NTM has been identified in many immunocompromised and immunocompetent patients with significant pulmonary and extrapulmonary diseases.[2-4] In India, NTM isolation and identification rate in pulmonary diseases varied from 0.7% to 34% and the species reported were *M. avium*, *M.fortuitum*, *M.scrofulaceum*, etc.[5-7] The various species of the NTM are continuously being reported from western countries also. In USA, every year around 300 cases of MAC are reported from lymphadenitis cases and other diseases (skin, soft tissue, tendons and joints). Since 1980, in US the association of MAC in AIDS patients is well known which has gone up to 37,000 cases in 1994 and *M. kansasii* reported as the second most common NTM that produces diseases in immunocompromised and immunocompetent patients.[8]

Till recently, NTMs were construed as laboratory or environmental contaminants. Thus, not getting due attention as a pathogenic organism. In most of the Indian studies, *Mycobacterium*

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tuberculosis (*M. tuberculosis*) has been found to be a major cause of mycobacterial infection and a portion of NTM has been considered low.[9] In India tuberculosis is diagnosed through smear examination of sputum. In this situation the infections caused by NTM are left undiagnosed or under-reported due to lack of culture and identification facilities of Mycobacterium in most of the laboratories. The NTMs are often resistant to drugs used for treating *Mycobacterium tuberculosis complex* (MTBC) which helps falsely conclude the patients as 'multidrug resistant tuberculosis (MDRTB)' who correspondingly take the treatment of 'MDRTB'. The aim of the study was to find NTMs in positive cultures and identify them upto species level.

MATERIAL AND METHODS

The study was conducted in the Department of Microbiology at LRS Institute of TB & Respiratory Diseases. The Institute has a National Reference Microbiology Laboratory engaged in smear microscopy, culture, drug sensitivity testing (DST) and implementing the DOTS and DOTS plus programmes catering to a population of around 1.3 million with the help of chest clinics at peripheral level. During Jan 2009-June 2011, a total of 15581 samples consisting of sputum (11945), Pleural fluid/pus (1540), Pus (835), Bronchial wash (521), Lymphnode aspirate (612), Ascitic fluid (91) and CSF (37), were processed for isolation and identification of mycobacterium.

The specimens were collected and processed by N-acetyl L cysteine – sodium hydroxide (NALC - NaOH) method, and inoculated in Lowenstein Jensen (LJ medium or Mycobacterium growth indicator tube (MGIT) culture tube as per clinician's request.[10,11] The LJ medium was incubated at 37°C for eight weeks and examined once in a week. In MGIT culture, the positive mycobacterium was identified by detection of fluorescence. Once tubes flagged as positive by the MGIT 960 instrument, it was confirmed by Ziehl-Neelsen staining and positive cultures were identified to species level after sub-culturing on solid LJ media. Each batch of the culture was accompanied with positive and negative control tube.

The positive cultures were screened by initial four biochemical tests, i.e. Niacin, Nitrate, heat resistant catalase test (HRCT) and para- nitro benzoic acid (PNB) test to differentiate the growth into MTBC and NTM. The NTMs were further identified to species level by morphological character and biochemical tests, i.e growth morphology, growth rate, growth at 25°C, 37°C and 44°C, pigment production in dark (schotochromogen), pigment production on exposure of light (photochromogen), no pigment production (non-chromogen), semi-quantitative Catalase test (SQCT), Thiophene2-carboxylic acid hydrazide (TCH) Susceptibility Test, Tween hydrolysis, Aryl sulphatase test (three days and 14 days), Sodium chloride tolerance test, Pyrazinamide test (four and seven days), iron uptake and growth on MacConkey agar.[13,14]

All the identification tests were standardized and monitored by positive and negative controls. The standard strains *M.fortuitum* (ATCC 6841), *M.chelonae* (ATCC19539), *M.smegmatis (*ATCC700084), *M.gordonae* (ATCC 35756), *M.avium-interacellulare* (ATCC13950), *M.kansasii* (ATCC 12478), *M.scrofulaceum* (ATCC 19698), *H37Rv* (ATCC 19977) were obtained from JALMA, Agra and were used in this study.

RESULTS

Amongst the 4104 cultures, preliminary identification results showed that 60(0.38%) isolates were identified as non-tuberculous mycobacteria and 4044 (25.95%) were categorized as MTBC (Table-1). The NTMs were isolated from various specimens, i.e sputum (22/15581, 0.14%), pleural pus (13/15581, 0.08%), lymph node aspirate (12/15581, 0.07%), pleural fluid (4/15581, 0.02%), bronchial wash (5/15581, 0.03%), pus (2/15581, 0.01%), CSF (1/15581, 0.006%) and ascitic fluid (1/15581, 0.006%) (Table-2).

Table 1: Mycobacterial culture results of clinical specimens

Cultures	Numbers	Percentage
Culture in LJ/MGIT	15581	100%
Mycobacterium positive cultures	4104	26.33%
M. Tb complexes	4044	25.95%
NTM	60	0.38%
Pulmonary NTM	44	0.28%
Extra-pulmonary NTM	16	0.10%

LJ = Lowenstein Jensen,
MGIT = Mycobacterium growth indicator tube,
M.Tb =Mycobacterium tuberculosis,
NTM = Non-tuberculous mycobacterium

In the present study, twenty one different species of non-tuberculous mycobacterium were identified, of which 13 were common in both pulmonary and extra-pulmonary specimens whereas eight species were found only in extra-pulmonary specimens (Table-2). On the basis of growth rate, growth characteristics and pigment production, 60 NTMs were categorized into all the four groups of Runyon classification. The maximum number of NTM found was in Gr111(31) followed by GrIV(16), Gr 11(08) and Gr 1(5) (Table-3). In this study, *M.simiae*(07) and *M.avium*(06) from the Group 111 were the common mycobacteria identified followed by five isolates each of *M.kansasii, M.gordonae,*

Table 2: Number of non-tuberculous mycobacterial species in clinical samples

Specimen	Bron-washing	Lymph node	pleural pus	Pl-fluid	CSF	Pus	Ascitic fluid	Sputum	Total
M. pheli	-	1	1	-	1	-	-	2	5
M.simiae	**1**	1	-	2	-	-	-	3	7
M.avium	**1**	1	1	-	-	-	-	3	6
M.fortuitum	-	1	1	1	-	-	-	2	5
M.chelonae	**1**	1	1	-	-	-	-	2	5
M. kansasii	-	1	1	1	-	-	-	2	5
M.gordonae	-	2	1	-	-	-	-	2	5
M.terrae	**1**	1	1	-	-	-	-	1	4
M.vaccae	-	-	1	-	-	-	-	1	2
M.malmoensae	-	-	1	-	-	-	-	1	2
M.trivale	-	1	1	-	-	-	-	-	2
M.flavescens	-	-	1	-	-	-	-	1	2
M.szulgae	**1**	-	1	-	-	-	-	-	2
M.triplex	-	-	-	-	-	-	-	1	1
M.mucogenicum	-	-	1	-	-	-	-	-	1
M.tuscae	-	1	-	-	-	-	-	-	1
M.septicum	-	1	-	-	-	-	-	-	1
M.scrofullacaeum	-	-	-	-	-	-	-	1	1
M.intracellulare	-	-	-	-	-	-	1	-	1
M.xenopi	-	-	-	-	-	1	-	-	1
M.ulcerans	-	-	-	-	-	1	-	-	1
Total	**5**	12	13	4	1	2	1	22	60

Pl.flu; pleural fluid, Bronch wash; bronchial wash, CSF; cerebero spinal fluid.

Table 3: Distribution of NTM isolates according to runyongroup N=60

Runyon Group	Species	No of isolates	%age of NTM
Group1	*M.kansasii*	05	8.33
Group 11	*M.gordonae*	05	8.33
	M.szulgai	02	3.33
	M.scrofulaceum	01	1.66
Group 111	*M.simiae*	07	11.66
	M.avium	06	10.00
	M.terrae	04	6.66
	M.malmoensae	02	1.66
	M .trivale	02	3.33
	M.vaccae	02	3.33
	M.flavescens	02	1.66
	M.intercellulare	01	
	M.xenopi	01	
	M.tusciae	01	1.66
	M.triplex	01	1.66
	M.ulcerans	01	
	M.septicum	01	1.66
Group 1V	*M.fortuitum*	05	8.33
	M.chelonae	05	8.33
	M.pheli	05	8.33
	M.mucogenicum	01	1.33
Total		60	

M.fortuitum, M. chelonae, M.pheli from the Runyon groups I, II and IV respectively (Table-3). In this study, no mixed or dual infection of mycobacterium had been observed.

DISCUSSION

During this comprehensive study, non-tuberculous mycobacteria were identified and described at a tertiary care institute having laboratory of international repute. The present study showed that 0.38% of mycobacterial strains were identified as NTM. Thus, this result showed that 1.16% of the total positive cultures were non-tuberculous mycobacteria and 98.63% were *M.tb* complex. Jesudason *et al* in his study showed that 3.86% were NTM and 96.13% strains were identified as *M.tb* complex amongst the culture positive mycobacterial growth. Karak *et al* from Kolkata have reported an NTM prevalence of 17.4% from sputum specimens in patients with fibrocavitary diseases. This was comparatively higher than reports of other workers including ours. Chakrabarthi *et al* from Chandigarh documented NTM isolation rate of 7.4% from various clinical specimens and *M.fortuitum* was the commonest isolate. Paramasivam *et al* from Chennai, South India has reported 8.6% of NTM from sputum specimens of patients in BCG trial area. *M. aviumintracellulare* was the species most frequently isolated in their study. Das *et al* reported isolation of 8.3% NTM from various clinical specimens from Delhi and Kasauli.[5,15-17]

The study from the other nations showed that the number of NTM identified were 8.3/100000 in Europe, 6.2/100000 in North America, 7.2/100000 in Australia and 12.6/100000 in Ontario, Canada and 15/100000 in Asia.[18] The common NTM species reported by developed nations were *M. avium, M.kansasii* and *M.gordonae*.[20] In contrast to them, in the present study, *M.simiae* (11.66%) was found to be the commonest NTM species along with other common species, i.e *M. avium*(10.00%), *M. kansasii*(8.33%), *M. gordonae* (8.33%) and *M. terrae* (6.66%). MAC and *M.simiae* have been isolated and reported by Narang *et al* from blood of AIDS patients.[21] Jesudason *et al* from South India observed that *M. chelonae* and *M. fortuitum* accounted for 67% of the total NTM isolates along with others, i.e *M. szulgai, M. terrae, M. scrofulaceum, M. flavescens, M. gordonae, M. simiae* and *M. smegmatis*.[22] This is in contrast to our report where 56% NTM belong to the slow grower group of class 111 as per runyon classification. In common with our study, Meena *et al* from Amritsar reported that 54% (approx) were slow grower mycobacterium strains which included *M. interacellulare* (15.4%), *M.kansasii* (7.7%), *M. gordonae* (7.7%) *and M. terrae* (15.4%).[20] They identified 46% of total NTM isolates belonging to the runyon group 111 and this trend has been observed in other Indian studies also.[23,24,16,17]

M.simiae has been identified as the most common NTM species in this study. Report published by Cook JL in British medical bulletin 2010 described that *M.simiae* is more common in arid region and is a common NTM species found in southwest USA, Cuba and Israel.[20] The temperature of Delhi is also warm, airy and dry supporting the growth of *M.simiae*. Rapidly growing mycobacteria are also the major components of NTM species. Reports from the Asian region (Taiwan, China, Singapore, etc.) showed that 16% of the total NTM are rapid growers i.e *M.fortuitum, M.abscessus* and *M.chelonae*.[25] In this study also, almost 30% of the NTM were identified as rapid growers consisting of *M.fortuitum*(8.33%), *M.chelonae*(8.33%), *M.pheli*(8.33%) and *M.mucogenicum* (1.33%). Jesudason *et al* described 54% of rapid growers which included *M.fortuitum* (41%) and *M.chelonae* (13%). Marras *et al* described 13% of rapid growers which include *M.abscessus, M.fortuitum and M.chelonae*.[22]

In this study, 45% of NTMs were from sputum and bronchial wash samples. The rest of the 55% of the NTM were isolated from lymphnode aspirates, empyema, pleural fluid, cerebro spinal fluid, pus and ascitic fluid. Li *et al* showed that a significant number of NTMs were isolated from sterile sites, i.e. surgical tissues, bronchial washing fluid, bronchial alveolar lavage fluid and others.[26] Other researchers also showed that different NTMs may cause localized pulmonary diseases, lymphadenitis, soft tissue infection, infection of joints/bones, bursae, skin ulcers and generalized diseases in leukemia and transplant patients.[27,28]

The fact that NTM are omnipresent, isolation of NTM from respiratory tract does not indicate that they are pathogenic. The drawback of the present study was that results were not co-related with clinical picture and radiological findings. A detailed research is required so that pathogen potential of NTM associated pulmonary and extra-pulmonary diseases can be proved with more certainty.

CONCLUSION

The isolation of NTM from various clinical samples indicated that it may be the cause of pulmonary diseases as well as extra-pulmonary diseases. Elaborate and focused studies are needed to differentiate NTM amongst commensal/colonizer, pathogen and laboratory contaminants and to see its impact in many diseases and follow up of patients where to conclude the outcome of the disease.

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Original Article

DIAGNOSTIC ROLE OF MGIT CULTURE OF BAL SAMPLES IN SPUTUM SMEAR-NEGATIVE PULMONARY TUBERCULOSIS*

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Summary

***Background*:** In view of the diagnostic difficulties associated with sputum- negative pulmonary TB (PTB), we aimed at exploring if bronchoalveolar lavage (BAL) samples can be subjected to smear- microscopy and rapid mycobacterial culture (by Mycobacterial Growth Indicator Tube (MGIT) method) to achieve improved diagnosis of this condition.

***Methods*:** Patients presenting with clinico-radiological features suggestive of pulmonary tuberculosis and whose sputum smears were negative for acid- fast bacilli (AFB) or who could not expectorate sputum were prospectively enrolled in this study. BAL samples collected from them were subjected to smear- microscopy for AFB and micro-MGIT culture. BAL samples were also inoculated on Lowenstein- Jensen (LJ) slants.

***Results*:** A total of 105 patients (74 males) were recruited in the study, with a mean (±SD) age of 51 (± 15) years. The diagnosis of PTB was made in 52 patients on the basis of clinico- radiological presentation, with or without microbiological confirmation. Thirty- four patients (65.4 %) had microbiologically confirmed PTB. Of them, AFB were detected in 12 BAL samples, while culture- positivity was noted in 24 and 27 patients by the LJ and MGIT methods respectively. Inter-test agreement between the LJ and MGIT methods was found to be significant (ê= 0.655; p= <0.001). However, the mean time to positivity was significantly lower for the MGIT method than for the LJ method (p= <0.001).

***Conclusion*:** Examination of BAL samples by smear- microscopy and micro-MGIT culture can, therefore, provide a rapid and definitive diagnosis of PTB in sputum- negative patients. **[*Indian J Tuberc 2013; 60:* 77 - 82]**

***Key words*:** MGIT, Micro-MGIT, Smear negative pulmonary tuberculosis, Bronchoscopy

INTRODUCTION

Tuberculosis (TB) is a major public health problem worldwide accounting for an estimated annual incidence of 9.27 million cases and 1.32 million deaths[1]. Detection of Acid Fast Bacilli (AFB) in sputum samples constitutes the mainstay of diagnosis in this disease[2]. However this method has a low sensitivity and has little value in patients who do not expectorate significant amount of sputum spontaneously[3, 4]. It has been reported that approximately 25-30 % of adult patients with suspected pulmonary tuberculosis (PTB) does not produce sputum spontaneously or have negative AFB smears[5]. With increase in the prevalence of TB-HIV co-infection, a rise in the proportion of sputum-negative PTB patients is anticipated[5]. In view of the difficulty in diagnosing these cases, they are often treated empirically, which may result in unnecessary cost, drug toxicity and worsening of clinical condition in patients suffering from alternative respiratory diseases like malignancy, pneumonia, interstitial lung disease and bronchiectesis.

Role of various alternative samples has been explored in diagnosing these patients, including bronchial aspirate, bronchial brushing, transbronchial lung biopsy, induced sputum with 3% NaCl and gastric aspirate[6-11]. Most of these studies have used conventional LJ medium for culture of bronchoscopic samples, which takes six to eight weeks for confirming the diagnosis. Recently some studies have reported the utility of performing PCR in these samples for the diagnosis of these patients [12-15]. But the technical sophistication and high cost involved in PCR prevent its widespread application in resource- poor settings. In view of recent studies reporting the usefulness of performing rapid

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mycobacterial culture on sputum samples, we undertook this study to analyse if BAL samples can be subjected to smear- microscopy and rapid MGIT culture to achieve an improved diagnosis of PTB in sputum- negative patients. In order to evaluate the applicability of the MGIT method to resource- poor settings, we used older manual system, requiring tubes to be examined for fluorescence under 365nm wavelength UV light source fluorescence detector. Though requiring more technical time, the manual system is affordable for laboratories with a smaller budget. We compared its results with culture on LJ medium.

METHODS

Consecutive patients above 18 years of age who attended Pulmonary Medicine OPD/IPD of Himalayan Institute of Medical Sciences, Dehradun (Uttarakhand) with a cough of at least two weeks' duration were subjected to two sputum examinations for AFB as per RNTCP guidelines. Antitubercular treatment (ATT) under DOTS was started if, sputum examination for AFB was found positive and only patients who were found to be sputum- negative or were unable to expectorate, were included in the study for bronchoscopy. The study was carried out over a period of twelve months, from August 2009 to July 2010. The study protocol was approved by the institutional ethics committee and written informed consent was recorded from each of the study subjects. Patients with known pregnancy, signs of respiratory and cardiac failure, pleural effusion, active haemoptysis, significant hypoxemia and HIV co-infection were excluded from the study.

BAL samples were collected from each of the recruited patients aseptically with the help of flexible bronchoscope (Olympus Corporation; BF type TE2), attached to a light source (Olympus CLK-4) and digital signal processing camera. The selection of the site for collection of BAL fluid was guided by prior imaging studies and local inspection of the disease site. As advocated by Jourdain *et al*, no endobronchial suction was attempted during the advancement of the bronchoscope to avoid contamination with upper airway flora [16]. Twenty milliliter aliquots of sterile normal saline were injected into the involved lobe, up to a maximum volume of 100 ml. Twenty to thirty milliliters of BAL fluid were collected from the involved lobe. BAL samples were transferred to 15 ml screw-capped tubes, incubated at room temperature for 15 minutes and shaken by hand at regular intervals.

Barring seven patients in whom obvious growth was observed on bronchoscopy, BAL samples of the remaining patients were processed for mycobacterial smear- examination and culture. All specimens were decontaminated and digested using the BBL MycoPrep Reagent (Becton Dickinson) containing N-acetyl –L-cysteine- 2% sodium hydroxide (NALC-NaOH). For each specimen, equal volumes (about 1 ml each) of reagent and specimen were pipetted into a centrifuge tube, vortexed briefly and allowed to stand at room temperature for 15 minutes. The BBL MycoPrep Phosphate Buffer (pH6.8) was added to the 10 ml mark on the centrifuge tube and the resulting mixture was centrifuged at 3,000 rpm for 15 minutes. The supernatant fluid was discarded. A portion (0.5ml) of the processed specimen was inoculated into each BBL MGIT tube together with BACTEC MGIT Growth supplement (oleic acid-albumindextrose-catalase) and BBL MGIT PANTA antibiotic mixture (polymyxin B, amphotericin B, nalidixic acid, trimethoprim, and azlocillin).The BBL MGIT tubes were incubated at 37^0C and examined daily in a 365nm wavelength UV light source fluorescence detector. Small amount of sediment was used to inoculate a slant of LJ medium. All LJ slants were incubated at 37^0C and examined daily until the appearance of colonies resembling mycobacteria. ZN staining was carried out on the colonies to identify.

ATT was started in confirmed (smear and/ or culture positive) patients who were not confirmed even after BAL but clinico-radiologically strongly suggestive of tuberculosis. We observed such patients for initial two months and if found improvement, labelled them as probable tuberculosis. Inactive PTB was considered to be present if AFB smear and culture results were negative, chest radiographic findings were consistent with healed tuberculosis and radiological change was not observed after two months of follow-up.

Statistical Analysis

McNemar's test was applied to determine if the difference in culture- positivity between smear-positive and smear- negative samples was statistically significant. Inter-test agreement between MGIT and LJ culture systems was determined by using the kappa-test. Analysis for the difference in sensitivity between the two methods of culture was done by using the z test for proportions. Unpaired t test was used to examine if the time taken for culture-positivity in the two culture methods was significantly different or not. All the statistical tests performed were two-tailed and p value <0.05 was taken as significant. SPSS version 17.0 was used for the statistical analysis.

RESULTS

A total of 112 patients were recruited in the study, of whom seven patients did not complete the study protocol and, hence, were excluded from analysis. The study group included 105 patients (74 males), with a mean (± SD) age of 51 (± 15) years. All the patients were suffering from cough of more than two weeks' duration and were smear- negative for AFB on performing microscopy of their sputum samples as per RNTCP protocol. Diagnostic bronchoscopy, followed by microscopy and culture of BAL samples, and chest radiography were undertaken in each of these patients. Fifty-two patients were diagnosed to be suffering from pulmonary tuberculosis, based on these microbiological and

Table 1: Final diagnosis made in the 105 smear negative suspects of pulmonary tuberculosis

	TB (n= 52)	**Other than active tuberculosis (n= 53)**	**P value**
Disease Distribution	Confirmed TB* =34 Probable TB # = 18	Old PTB= 18 Bronchogenic Ca=7 Pneumonia=12 Bronchiectesis =5 ILD= 3 NHL=2 Aspergilloma=2 Sarcoidosis =3 Teratoma= 1	
Age distribution (Mean ± SD)	49 ± 15	52 ± 16	
Gender Distribution (M/F)	31/21	38/15	
H/O smoking	33 (63.4)	35 (66.0)	0.782
Clinical presentation			
Fever	40 (76.9)	40 (75.4)	0.861
Hemoptysis	16 (30.7)	21 39.6)	0.342
Expectoration>2ml	38 (73.0)	34 (64.1)	0.324
Bronchoscopic Findings			
Normal bronchial tree	25 (48.0)	22 (41.5)	0.498
Normal bronchial tree with secretion	13 (25.0)	17 (32.0)	0.422
Normal bronchial tree with distortion	5 (9.6)	8 (15.0)	0.394
Growth	0 (0.0)	8 (15.0)	0.003
Erythema/ulceration/nodularity	19 (36.5)	11 (20.7)	0.073
Radiological Findings			
Cavitary disease	7 (13.4)	6 (11.3)	0.739
Extent of lesion			
Minimal	29 (55.7)	25 (47.1)	0.378
Moderate	13 (25.0)	18 (33.9)	0.314
Advanced	10 (19.20	10 (18.8)	0.962

* Confirmed TB = Smear and/or culture positive on BAL

Probable TB = patients who were not confirmed even after BAL but clinico-radiologically strongly suggestive of tuberculosis.

radiological parameters. Fifty three patients were diagnosed to be non-tubercular, as shown in Table-1. The clinico-radiological and bronchoscopic findings of the recruited subjects are shown in Table-1.

Of the 52 patients with tuberculosis, 12 were AFB smear- positive on examination of their BAL samples. Culture by LJ and MGIT methods yielded the growth of *M. tuberculosis* in 24 (46.1%) and 27 (51.9 %) patients respectively. In all, 30 (57.6%) patients were culture-positive and 34(65.3%) patients were positive for smear and/or culture examination. Culture-positivity was significantly higher among the smear- positive patients compared to the smear- negative ones (p= 0.017 for LJ culture and p= 0.003 for MGIT culture) (Table- 2). Inter-test agreement between the LJ and MGIT methods was also found to be significant (ê= 0.655; p= <0.001). No significant difference was observed in the sensitivity of the two culture techniques (p= 0.392). However, the mean time to positivity was 11.7 (SD= 4.1) days for the MGIT method, while the corresponding duration was 43.7 (SD= 3.1) days for the LJ method (p= <0.001). Eighteen patients, who were negative for both smear and culture examinations, were diagnosed on the basis of radiological lesions and response to empirical ATT. Analyzing the different covariates associated with smear and/ or culture positivity, we observed that presence of expectoration and cavitary lesions was more frequent in the microbiologically confirmed cases, than in the radiologically suggestive ones, though the difference did not reach the level of statistical significance (Table- 3).

Table 2: Isolation of *M. tuberculosis* from 52 BAL specimens on MGIT and LJ media

	Smear positive (%) (n= 12)	**Smear negative (%) (n= 40)**	**P value**
LJ +ve	7 (58. 3)	17 (42.5)	0.334
MGIT +ve	8 (66.7)	19 (47.5)	0.243

Table 3: Clinico-radiological and demographic profile of 52 diagnosed patients of smear negative PTB

Profile	**Confirmed PTB (n=34)** No (%)	**Probable PTB (n=18)** No (%)	**p value**
Age (mean)	18-72 yrs (50.14)	19-80 yrs (46.8)	
Gender (M/F)	18/16	13/5	
Clinical profile			
Fever	26(77.5)	14 (80.9)	0.915
Haemoptysis	10 (32.2)	6 (28.5)	0.770
Expect>2ml	25 (80.6)	13 (61.9)	0.919
ATT history	11 (35.4)	7 (33.3)	0.637
Radiological profile			
Cavitary lesion	6 (19.3)	1 (4.7)	0.224
Extent of lesion			
Minimal	17 (61.2)	12 (66.6)	0.249
Moderate	9 (19.3)	4 (28.5)	0.736
Advanced	8 (19.3)	2 (14.2)	0.279

DISCUSSION

In this paper, we have shown that performance of smear- microscopy and rapid mycobacterial culture on BAL samples leads to a significantly improved diagnostic yield in sputum-negative PTB patients. Moreover, compared to conventional LJ culture, there is a significant reduction in the time- to- culture- positivity with the incorporation of MGIT culture, which facilitates the earlier initiation of ATT in these patients.

Considering the relative paucity of diagnostic tools in sputum- negative PTB patients, several authors have explored the potential utility of bronchoscopic specimens in achieving a definitive diagnosis of PTB. Yuksekol *et al*[17]and Chan *et al*[18] have reported smear- positivity rates of 23% and 14% respectively in BAL samples, which is similar to the figures obtained in our study. However, higher values ranging from 38% to 65% have been reported in studies which have considered the cumulative diagnostic yields of multiple bronchoscopic specimens like bronchial aspirate, bronchial brushing, TBLB, and post-bronchoscopic sputum smears [19-21]. However, reports on the MGIT culture technique has been relatively limited in BAL samples obtained from sputum- negative PTB patients. We report a significant improvement (51.9% for MGIT *vs* 23% for smear) in the diagnostic sensitivity when this modality of culture is added to smear-examination of BAL samples. Combining both the modalities of culture, i.e. MGIT and LJ, the sensitivity increased further to 57.7%. Hence, use of MGIT on BAL samples of sputum- negative PTB patients helps to generate a definitive evidence of tuberculosis, which is quite useful considering the number of simulating respiratory conditions that may mimic the clinical presentation of these patients. The relatively earlier report obtained with MGIT culture (11.7 days *vs* 43.7 days) also offers obvious clinical advantages, in terms of earlier initiation of therapy and reduction in disease transmission by the patients. We obtained a sensitivity of 46.2% for LJ culture of BAL samples, which is consistent with earlier studies reporting sensitivity ranging from 46% to 56% [17,19,22,23]. Our mean value of 11.7 days for culture-positivity in MGIT system is also similar to other studies reporting mean duration of five to 21 days in sputum-negative specimens [24-29]. The most remarkable advantage with the recent methods of automated mycobacterial culture lies in their earlier detection of culture- positivity. Among them the earliest and most widely studied method, viz. BACTEC – 460 system, requires sophisticated instrumentation and the provision of safe handling and disposal of radioactive waste. Alternate methods like MGIT and MB Redox tube systems are based on detection of fluorescent or colorimetric signals and, hence, are free from the hazards of radioactive handling. In this study, we used a miniaturized, semi-automated, battery- operated version of the MGIT system, which is cost- effective and adjustable to the workload of a small- to medium- sized laboratory.

LIMITATIONS

Our study suffered from several limitations. Firstly, performing bronchoscopy following CT scan of the thorax might have improved the diagnostic yield of BAL specimens even further by allowing a better localization of the pulmonary lesion. But since it is not possible to perform CT scan in all suspected sputum- negative PTB patients in resource- poor settings, the same was not included as a part of the study protocol. Secondly, sputum examination, by MGIT culture, might have been a simpler and non- invasive method of evaluation in these patients. But since a major fraction of the recruited patients (approximately 27%) did not have significant expectoration and it was not possible to perform MGIT culture of both sputum and BAL samples, owing to resource- constraints, we decided to include only BAL samples in our study.

We, therefore, conclude that examination of BAL samples by smear-microscopy and MGIT culture can provide a rapid and definitive diagnosis of PTB in sputum-negative patients.

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Original Article

TUBERCULOSIS OF THE DUODENUM: CLINICAL PRESENTATION, DIAGNOSIS AND OUTCOME

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Summary

***Background*:** Duodenal tuberculosis accounts for <2% of abdominal tuberculosis and usually manifests with recurrent vomiting. Existing guidelines suggest surgery as the mainstay for both obtaining a definitive diagnosis as well as for therapy.

Aims: The aim of this prospective study was to describe the clinical presentation and usefulness of endoscopic techniques in the diagnosis and treatment of duodenal tuberculosis.

***Methods*:** Data of patients diagnosed to have duodenal tuberculosis over a three-year-period were analysed for age, presenting symptoms and outcome of therapy. Diagnosis was based on histological evidence of granulomatous inflammation along with unequivocal improvement in vomiting and other symptoms over six-eight weeks following a combination of anti-tubercular drug therapy and endoscopic balloon dilatation.

Results: Ten patients with recurrent vomiting (median age 27 years) were diagnosed to have duodenal tuberculosis. Significant narrowing was seen at endoscopy in nine patients with post bulbar area being the commonest site in five patients. Histological diagnosis of granulomatous duodenitis was possible in nine (90%) patients. Balloon dilatation achieved resumption of normal diet at a median duration of seven days (range 2-40). Symptomatic improvement was substantiated by a median increase in BMI of 5 kg/m^2 over the baseline value. Surgical intervention was not required in any patient.

***Conclusions*:** Recurrent vomiting due to gastric outlet obstruction is the commonest presentation of duodenal tuberculosis. Endoscopically, a histological diagnosis of granulomatous inflammation can be achieved in most of the patients. Endoscopic balloon dilatation coupled with anti-tubercular drug therapy is safe and effective treatment for this uncommon disease. **[*Indian J Tuberc 2013; 60:* 83 - 88]**

***Key words*:** Tuberculosis, Duodenum, Diagnosis, Outcome

INTRODUCTION

Tuberculosis continues to be a major public health problem in many countries around the world. Abdominal tuberculosis is the sixth most common site of extra-pulmonary tuberculosis.[1] The commonest site of abdominal tuberculosis remains the ileo-cecal region accounting for nearly 85% of all cases of abdominal tuberculosis.[2] Involvement of the stomach and duodenum is uncommon and accounts for 1-2% of all cases of abdominal tuberculosis.[1,3] These are generally considered together under the blanket term of gastroduodenal tuberculosis.[4-6] Management guidelines for gastroduodenal tuberculosis published a few years ago suggest that surgery is the mainstay for both diagnosis as well as for definitive treatment.[6] Although the disease is predominantly reported from South Asia, anecdotal cases have been reported from all parts of the world.[7-9]

The aim of this prospective study was to describe the clinical presentation and usefulness of endoscopic techniques in the diagnosis and treatment of the sub-group of patients having isolated disease of the duodenum. Our study questions the validity of the current guidelines for the management of gastroduodenal tuberculosis.

MATERIAL AND METHODS

An ongoing prospective study on tuberculosis of the stomach and duodenum was

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started in the department of Gastroenterology, GB Pant hospital, New Delhi in 2009 in an attempt to study the clinical presentation and natural history of tuberculosis at these uncommon sites. A part of this work highlighting the efficacy of endoscopic dilatation in patients with gastro-duodenal tuberculosis has been published recently by our group.[10] The current study is a sub-group analysis focused on the clinical presentation and outcome of duodenal tuberculosis alone. Data were analysed for age, presenting symptoms and the outcome of therapy.

Patients presenting with contiguous involvement of the stomach and duodenum were excluded from this analysis. Deformity of the pyloric ring as seen at endoscopy was considered as evidence of contiguous involvement of the stomach and duodenum; hence all the patients in this report had an anatomically intact pyloric ring as an inclusion criterion. A record was made of the morphological appearance and the site of involvement of the duodenum. Morphologically, the lesions were classified as hypertrophic, ulcerative or stricturing prior to multiple biopsy sampling (eight-ten pieces) from the involved site .The diagnosis of duodenal tuberculosis was made on the basis of pathologic lesions in the duodenum showing the presence of acid-fast bacilli (AFB) on Ziehl-Neelsen staining or tissue polymerase chain reaction (PCR) positivity for *Mycobacterium tuberculosis* on endoscopic biopsies. Where AFB were not documented, the presence of epithelioid granulomas in endoscopic biopsies coupled with an unequivocal response of vomiting and other constitutional symptoms to anti-tubercular therapy (ATT) within six-eight weeks of initiating therapy was also considered as a diagnostic criterion for duodenal tuberculosis. Patients showing luminal narrowing with granulomatous pathology or AFB on the biopsy were taken up for endoscopic balloon dilatation under fluoroscopic guidance using a side-viewing endoscope (Fujinon G5, Japan) and through the scope (TTS) balloons (Wilson Cook, NC, USA). Serial dilatation was done starting from a balloon size of 12 mm; the end point of dilatation was arbitrarily defined as successful dilation with 18 mm and 16 mm balloon for adults and children, respectively. Post dilatation, the approximate length of the stricture was measured by calculating the distance between the healthy mucosa on either side of the strictured segment on gradual withdrawal of the endoscope. All patients were admitted and monitored for complications after the dilatation. Oral feeds were introduced at 24 hours post dilatation after a check X-ray examination. Subsequently a record was made as to when the patient was able to resume his/her regular diet. All patients received four-drug anti-tubercular regimen (rifampicin, isoniazid, pyrazinamide, streptomycin) in the appropriate dosage during first two months followed by rifampicin and isoniazid in the continuation phase. We intentionally used injectable streptomycin as this is the only drug which would be unaffected by recurrent vomiting. Recurrence of vomiting, compliance and toxicity to the anti-tubercular drug therapy were monitored on each follow up visit. Dilatation was repeated if the patient had recurrence of vomiting after the initial dilatation. Chest skiagram and CT scan of the abdomen were done to document the presence of tuberculosis at extra-duodenal sites. Barium studies of the upper gastrointestinal tract were done in select cases only. History of prior treatment for pulmonary or extra-pulmonary tuberculosis was recorded. All patients were tested for human immunodeficiency virus (HIV) infection after obtaining an informed consent. Body mass index (BMI) was calculated for each patient prior to commencement of drug therapy; the measurement was repeated at three months and the delta (Ä) BMI was noted.

Ten age and sex matched patients diagnosed to have ileo-cecal tuberculosis were taken as controls whose BMI prior to initiation of the anti-tubercular therapy was compared with the study group. None of the control group of patients had recurrent vomiting at presentation.

Statistical methods: Continuous variables were expressed as median and range in view of the small sample size. Non parametric tests, Wilcoxon's signed-rank test and Mann Whitney U test were used to compare the difference in median values of paired and unpaired data respectively. A 'p' value of <0.05 was considered to be significant.

RESULTS

Over a span of three years, 10 patients (five males) were diagnosed to have duodenal tuberculosis at GB Pant hospital, New Delhi. The median age of the patients was 27 years (range 12-45 years). Recurrent vomiting was the dominant feature in all the 10 patients. The median duration of vomiting prior to diagnosis was three months (range 0.5-18 months). Prolonged fever of > 2 weeks at the time of presentation was noted in four (40%) patients. Appreciable weight loss was documented in all patients with a median value of 8 kg (range 6-13 kg) at the time of presentation to the hospital. The median value of BMI at presentation was 16.4 kg/m^2 (14.2-17.6) *versus* corresponding values of 19.4 kg/m^2 (15.6-27) in the control group of patients with ileo-cecal tuberculosis ($p < 0.05$). Three patients (30%) had a prior history of being treated for pulmonary tuberculosis in the past. None of the patients had HIV co-infection.

Transabdominal ultrasonography and abdominal CT scan were done in 10 and seven patients, respectively. Para-duodenal lymphnodes (>20 mm) were documented in six patients (Figure 1), whereas in four patients, there was no significant lymphadenopathy. Extra-duodenal disease involving retroperitoneal lymph nodes, jejunal and ascending colon was detected on CT abdomen in three patients. At endoscopy duodenal narrowing with ulceration was seen in all ten patients. The commonest site of involvement was the post bulbar area in five patients followed by the descending limb or second part in three patients (Figure 2) and third part of the duodenum in two patients. The narrowing was significant enough to preclude the passage of the gastroscope in nine of the 10 patients; in four patients, the lumen showed a pin hole size opening. Histological evidence of granulomatous inflammation (Figure 3) was documented in nine patients whereas in one patient tissue PCR was positive for *Mycobacterium tuberculosis*. AFB were not seen in the tissue biopsy specimens in any of the 10 patients. Therefore, a presumptive histological diagnosis of tuberculosis could be made in all the patients using endoscopic methods.

Endoscopic dilatation was successfully done in nine patients (Figure 4). The median number of sessions required were four (range 1-6). The length of stricture as measured by the scope withdrawal technique ranged between 1-2 cm in all the patients.

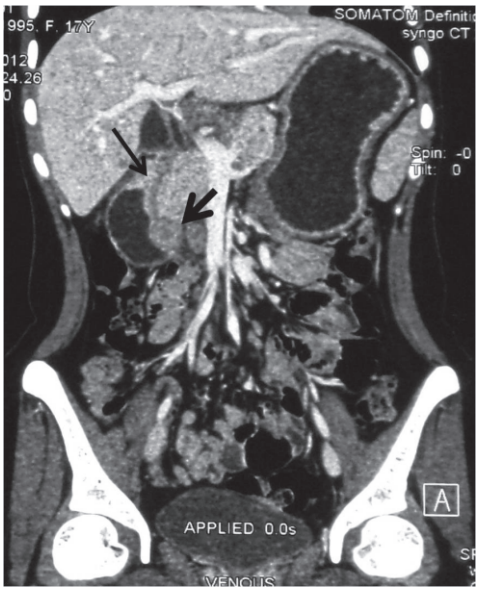

Figure 1: Abdominal CT scan image showing duodenal wall thickening (thin arrow) and enlarged para-duodenal lymphnodes (thick arrow)

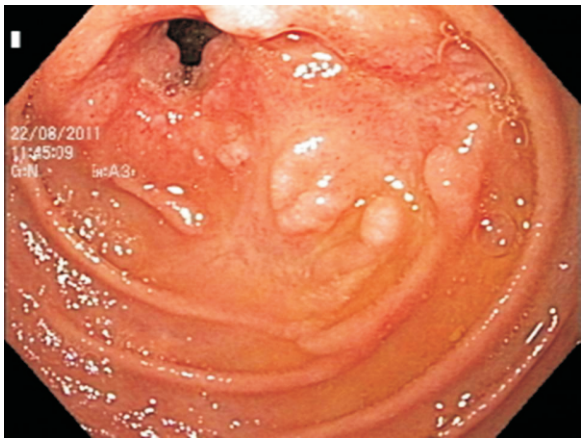

Figure 2: Endoscopic image from second part of duodenum showing areas of mucosal nodularity proximal to duodenal stricture before initiation of treatment

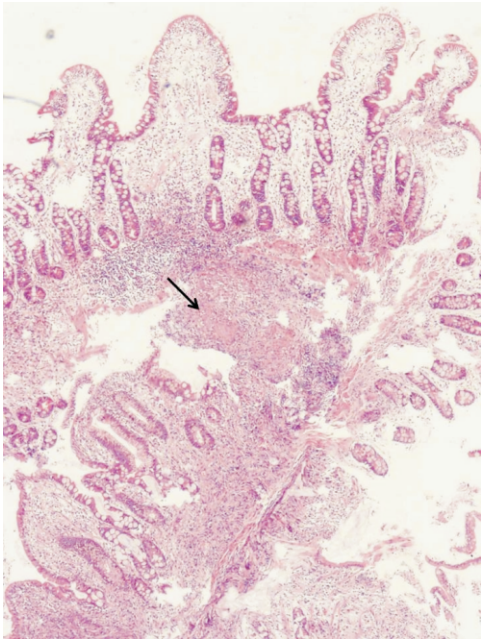

Figure 3: Histopathological section (haematoxylin and eosin stain, 100X) of duodenal biopsy showing granuloma (arrow)

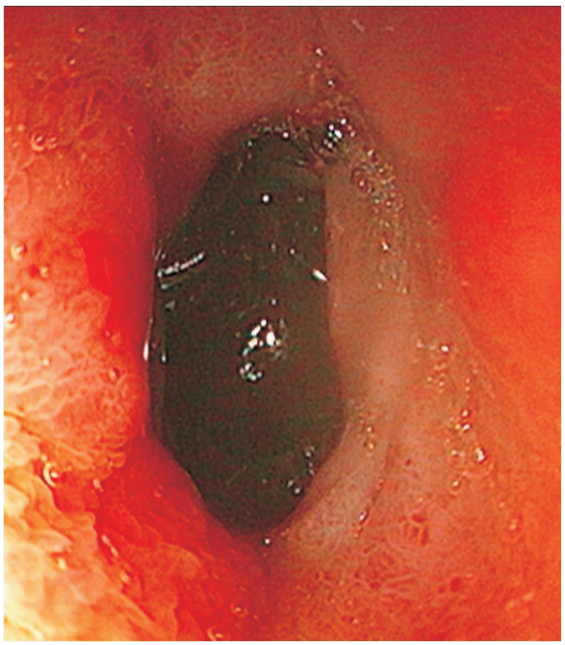

Figure 4: Endoscopic image from a patient with duodenal tuberculosis after endoscopic balloon dilatation showing nicely opened up duodenal stricture

Dilatation was not done in one patient who had a sub-clinical stricture as the scope could be passed across the stricture without much difficulty. A minor complication of retro-peritoneal perforation occurred in one patient which was managed conservatively.

The median follow up period was 10.5 months (range 2-13 months). The standard duration of the ATT was six months but in those patients where there was delayed resumption of the normal diet, duration of the anti-tubercular drug therapy was arbitrarily extended to nine months. All patients complied to the drug treatment for the stipulated period. None of the patients had any adverse drug reaction to the anti-tubercular drug therapy. All four patients with fever at presentation became afebrile within four weeks of therapy. No recurrence of vomiting was reported by any patient after four weeks of combination therapy of anti-tubercular drugs and balloon dilatation. The median time for resumption of normal diet was seven days (range 2-40 days). No patient was referred for surgical management. The median Ä BMI at three months was 5 kg/m^2 (range 1.1-6.5) which suggested a statistically significant change over the base line value ($p < 0.01$).

DISCUSSION

The duodenum is an uncommon site for tuberculosis even in endemic areas like India. Rao *et al*[6] reported a series of 23 patients seen over a period of 15 years at a tertiary referral centre in India. In another study from Delhi, duodenal tuberculosis accounted for <2% of 159 patients operated for abdominal tuberculosis.[3] A Medline search using the terms gastroduodenal tuberculosis, tuberculosis of the duodenum and granulomatous duodenitis yielded only six original articles related to this topic published in English medical literature till 2011. Expectedly, most of the published work on duodenal tuberculosis has come from the Indian sub-continent where it accounts for 2% of all abdominal tuberculosis.[1,3] It is essentially a disease of the young; nine of the ten (90%) patients in our study were less than 35

years of age with a median age of 27 years (range 12-45 years) which is not very different from the mean age of 34 years in the report by Rao *et al*.[6]

Recurrent vomiting over a short period of time is the cardinal symptom of duodenal tuberculosis. The median duration of vomiting prior to referral in our study was three months (range 0.5-18 months). The protracted vomiting results in severe nutritional depletion as is evident from the low median values of BMI (16.4 kg/m^2) at presentation. In this regard duodenal tuberculosis is different from the garden variety of abdominal tuberculosis (ileo-cecal) as the nutritional depletion is significantly lower in the latter despite the basic pathology being similar in both.

Two dogmas pertaining to duodenal tuberculosis need to be changed in the light of the new information from our study. Existing literature suggests that endoscopy is of little value in obtaining a specific histologic diagnosis in duodenal tuberculosis.[5,6,11,12] Three previous studies from India have shown the yield to be in the range of 0-10%[6,11,12] and hence the recommendation that surgery is essential for making the correct diagnosis. The yield of endoscopic biopsy from duodenal stricture may vary depending on the fact whether the duodenal mucosa is directly involved by the tubercular pathology or as a consequence of extrinsic compression by periduodenal lymphnodes. The low yield of endoscopic biopsy was the basis of recommending surgery as the primary modality for diagnosis in the recently published guidelines for management of gastro-duodenal tuberculosis.[6] Our previous report has argued against this dogma as we were able to show granulomatous inflammation using a combination of endoscopic biopsy and endoscopic mucosal resection (EMR) in more than 90% of the patients with a final diagnosis of gastro-duodenal tuberculosis.[10] In the current study, a histological diagnosis of granulomatous inflammation was obtained in all the ten patients. Although AFB were not seen in any of the tissue biopsy specimens, all patients had an unequivocal response to the combination of anti-tubercular drugs and endoscopic dilatation. We attribute the higher histological yield to the higher number of biopsies (8-10) and the better targeting of the lesions in our study. A high yield of endoscopic biopsy for demonstration of granulomatous inflammation in gastroduodenal tuberculosis has previously been reported by Jain *et al*[13] and therefore should not be considered as an isolated finding.

The second dogma pertains to the treatment of duodenal tuberculosis. Existing literature is heavily biased in favour of surgical management.[5,6,12] Surgery was required either for diagnosis or treatment in all but one of the 40 cases (97%) in two large series from India.[5,6] The patient composition however in both these reports was a combination of both gastric and duodenal tuberculosis. Majority of the patients underwent a gastrojejunostomy with or without a feeding jejunostomy and a truncal vagotomy. In contrast, our data clearly argues against a primary surgical management for this condition. Each of the 10 patients in our study was managed effectively (without recourse to surgery) with anti-tubercular drug therapy with or without endoscopic stricture dilatation. The efficacy of this approach is underscored by the fact that the patients were able to resume their normal diet within a median period of seven days (range 2-40 days) with only one minor complication of a retroperitoneal perforation. Complete amelioration of vomiting was seen in all 10 patients within a short period of 4-6 weeks after initiation of the definitive therapy. Two brief reports from India also support the case for endoscopic balloon dilatation for tubercular strictures.[14,15]

Duodenal strictures in the second and third parts of the duodenum are invariably concentric due to the fact that the duodenum is essentially like a hollow cylinder and the fibrotic stricture occludes the lumen in a centripetal fashion. The concentric nature of these strictures allows the guidewire to be placed beyond the strictured segment following which balloon dilatation can easily be done. The short length of these strictures (1-2 cm) makes them ideal candidates for endoscopic dilatation. Our observation on the length

of tubercular strictures is in agreement with the earlier study by Tandon and Prakash[3] who reported that tubercular strictures are usually <3 cm in length. The end point of balloon dilatation (18mm) though arbitrary is in line with the existing recommendation for balloon dilatation of benign gastric outlet obstruction.[16] The efficacy of balloon dilatation is further substantiated by the complete amelioration of symptoms during the follow up in our study.

In conclusion, duodenal tuberculosis is an uncommon disease manifesting most often with features of gastric outlet obstruction resulting in severe malnutrition. The commonest site of involvement is the post bulbar area followed by the second and third parts of the duodenum. Histologic diagnosis can be achieved in most patients with multiple biopsy sampling. Anti-tubercular drug therapy in combination with endoscopic balloon dilatation should be the initial therapy of choice as it is effective, safe and relatively less invasive as compared to surgery. Surgical options should be reserved only for those patients who fail the combination therapy. Our study provides compelling evidence to revise the current guidelines for management of duodenal tuberculosis.

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Original Article

RELIABILITY OF INVOLVING COMMUNITY VOLUNTEERS AS DOT PROVIDERS IN DOTS STRATEGY UNDER RNTCP

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Summary

***Set up*:** One Tuberculosis Unit (TU) in Tiruvallur district, Tamil Nadu, where Tuberculosis (TB) patients treated under Directly Observed Treatment Short Course (DOTS) programme.

***Objective*:** To assess the reliability and accountability of Government health workers and community volunteers as DOT Providers (DPs) and to assess treatment outcome and problems encountered by patients managed by different DPs and the acceptability of community providers in the RNTCP.

***Methods*:** The 189 DPs in the study area during the first and second quarters of 2005 and 303 patients who were treated by these DPs were interviewed. Univariate analyses were used to identify the factors influencing the success rate.

***Results*:** Of 303 patients treated, the success rates of the patients treated by Government DOT providers (GDP) and community DOT providers (CDP) were 85.3% (209/245) and 86.2% (50/58) respectively. The difference in the success rates by GDP and CDP was not statistically significant. Among the 259 patients who successfully completed treatment, 82% (172/209) under GDP and 84% (42/50) under CDP were regular for treatment and there was no association between the type of DOT providers and regularity of treatment.

***Conclusion*:** Community volunteers could be inducted as DPs into the DOTS strategy for efficient supervision and management of the patients. **[*Indian J Tuberc 2013; 60:* 89 - 94]**

***Key words*:** Community volunteers, DOTS, Tuberculosis

INTRODUCTION

In India, tuberculosis (TB) is a major public health problem and controlling TB is a tremendous challenge in our country. The Revised National Tuberculosis Control Programme (RNTCP), an application of the globally accepted WHO recommended Directly Observed Treatment Short-course (DOTS) strategy was implemented in 1993 on a pilot basis, rapidly expanded from 1997 and achieved nation-wide coverage in March 2006[1,2]. DOTS is the most effective and reliable strategy available for controlling TB. Monitoring, support and supervision of patients are necessary for treatment success and it also ensures the health care providers' accountability of convincing the patients that TB is curable with adequate treatment. TB patients who are not adhering to treatment have the chance of decrease in cure, increase in risk of relapse after treatment and to become drug resistant[3]. A DOT provider is a trained health worker or other designated individual who provides the prescribed TB drugs and observes that the patients swallow every dose and ensures the treatment for the entire course. A DOT provider (DPs) can be anybody (a health worker or a community-based volunteer) who is accessible and acceptable to the patient and accountable to the health system and who is not a family member. The treatment support by DPs and their involvement decrease default rate of the patients and improve treatment compliance. Their sustained efforts in motivating and supervising the drug intake of the TB patients during the treatment period of six to eight months help to increase the success rate and attain the programme target of 85% cure rate[4].

Government of Tamil Nadu has identified Village Health Nurses (VHN), Health Inspectors (HI) and Community Nutrition Workers as DOT Providers

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(DPs). Their routine schedule does not permit them to be in the same village every day hence they are not able to provide DOT on regular basis. After having recognized the problems, decentralizing TB Control measures beyond health facility by inducting Community Volunteers to act as DPs to facilitate administration of regular and complete treatment has been initiated. Identifying good DPs is a challenge. The objective of the study is to assess the reliability and accountability of government health workers and community volunteers as DPs and to assess treatment outcome and problems encountered by patients managed by different DOT providers and their acceptability of community providers in the RNTCP.

MATERIAL AND METHODS

National Institute for Research in Tuberculosis (NIRT) (formerly TB Research Centre) in collaboration with Government of Tamil Nadu undertook a project on conducting operational research on the key aspects of DOTS strategy in Tiruvallur district covering a population of 5.8 lakhs. During January 2005 -June 2005, the DPs in the study area were visited by trained field workers of NIRT. They were interviewed by using a semi-structured questionnaire to elicit information on their practices and problems encountered while acting as a DOT Provider. All patients who were treated by these DPs at the time were also interviewed.

The trained field workers interviewed 108 DPs and 303 TB patients and collected information about DPs on socio-economic characteristics, problems faced as DPs, their activities, their workload in term of time, category and number of patients, distance travelled to meet a patient, and various factors related to performance of their responsibilities. The 189 DPs were classified into two different categories namely; Government DPs (GDP), including Anganwadi workers (AWW) and community DPs (CDP). The 303 patients were also interviewed to investigate about their socio-economic characteristics, the type of DPs chosen, their DOT centre, whether taking drugs under supervision, any problem in taking drugs under supervision, time spent by DPs with them, distance travelled from their homes to DPs place, attitude of DPs with them, complaining of side-effects to DPs and their feeling about the treatment taken from DPs. The patient's data regarding treatment outcome, regularity, disease types, category, initial smear status and place of diagnosis were collected from treatment register maintained at the TB unit. Treatment success is estimated as the number of patients cured or completed treatment under the supervision of DPs. In RNTCP, the expected time duration to complete treatment for a new smear positive TB patient is within seven months (six months + one month grace period). The treatment is extended to eight months (seven months + one month grace period) for the patients whose sputum does not convert at two months, by extending the intensive phase by one more month. Patients were considered as irregular if they took longer than RNTCP norm to complete treatment[5].

Data were scrutinized after keying in twice in order to ensure accuracy, and further corrected for discrepancy and missing information. Univariate analysis was carried out using SPSS 14.0 Version. In univariate analysis, crude Odds Ratio (OR) and 95% C.I were used for interpretation of various factors for success rate of patients treated under the supervision of GDP and CDP. Chi-square test of significance was used to test the association between different factors. Fisher's exact test was used when the expected frequency was less than five. Statistical significance was set for p value < 0.05.

RESULTS

In all, 303 patients were included in the study. Of these, 245 patients were under the supervision of 137 GDPs and the remaining 58 patients under 52 CDPs. The baseline characteristics of all 189 DPs are shown in Table 1. Majority of DPs (84%) were females; 65% less than 45 years old; 82% married; and 91% literate. Majority of DPs (82%) were given RNTCP training. Very few (10%) only faced problems when they were working as DPs. Almost all the DPs (96%) would like to continue to work as community DPs in future also.

Of 137 GDPs, 16 (11.7%) reported that they faced problems like domestic, patients' non-cooperation, inability to contact patients on due date, lack of storage facility for medicines and interference with their work compared to two (3.8%) of 52 CDPs.

Table 1: Characteristics of DOTS Providers

Factors	Total (N = 189)	CDP (N = 52)	GDP (N = 137)
Sex			
Male	31 (16.4)	18 (34.6)	13 (9.5)
Female	158 (83.6)	34 (65.4)	124 (90.5)
Age			
≤ 45yrs	123 (65.1)	41 (78.8)	82 (59.9)
> 45 yrs	66 (34.9)	11 (21.2)	55 (40.1)
Marital Status			
Married	155 (82.0)	40 (76.9)	115 (83.9)
Others	34 (18.0)	12 (23.1)	22 (16.1)
Education			
Illiterate	17 (9.0)	6 (11.5)	11 (8.0)
Literate	172 (91.0)	46(88.5)	126 (92.0)
How long worked as DP			
<1 year	67 (35.4)	41 (78.8)	26 (19.0)
>=1 year	122 (64.6)	11 (21.2)	111 (81.0)
Given RNTCP training			
No	33 (17.5)	22 (42.3)	11(8.0)
Yes	156 (82.5)	30 (57.7)	126 (92.0)
Patients taking drugs under observation			
Yes	113 (59.8)	32 (61.5)	81(59.1)
No	76 (40.2)	20 (38.5)	56 (40.9)
Problems faced as a DP			
No	171 (90.5)	50 (96.2)	121(88.3)
Yes	18 (9.5)	2 (3.8)	16 (11.7)
Patients' complaints of side-effects			
No	79 (41.8)	26 (50.0)	53 (38.7)
Yes	110 (58.2)	26 (50.0)	84 (61.3)
Default retrieval action			
No	70 (37.0)	29 (55.8)	41 (29.9)
Yes	119 (63.0)	23 (44.2)	96 (70.1)
Willing to continue as CDP in future			
No	7 (3.7)	6 (11.5)	1 (0.7)
Yes	182(96.3)	46 (88.5)	136 (99.3)

The corresponding figures for taking retrieval action were 70.1% (97 of 137) and 44.2% (23 of 52) respectively.

Of 303 TB patients treated under DOT, 69% of the patients were males; 61% literate and 63% ≤ 45 years' old. More than half (55%) of the patients mentioned some problems in taking drugs under supervision. 63 patients (20%) mentioned drug-related problems and 61 (20%) mentioned work-related problems while taking treatment under DPs' supervision and 13% of the patients (14% of those under GDPs and 10% of those under CDPs) mentioned that DPs' place was more than three kilometers from their residence.

Of the 303 patients interviewed, 245 (80.9%) were treated under the supervision of GDP

and the rest by CDP. Almost all patients (238/245 under GDPs and 56/58 under CDPs) were satisfied with the treatment taken from their DPs. Among the 245 patients, 23 (9.4%) defaulted, five (2%) expired and eight (3.3%) failed to treatment and the corresponding figures for the 58 patients treated by CDP were five (8.6%), one (1.7%) and two (3.4%). The success rates of patients treated by these DPs were 85.3% (209/245) and 86.2% (50/58) respectively; the overall success rate being 85.5%. The difference in the success rates by GDP and CDP was not statistically significant ($\div^2$ = 0, p = 0.974). The distribution of socio-demographic factors for success rate of patients supervised by GDP and CDP is set out in Table 2. It could be observed that none of the factors of the patients under supervision of GDP and CDP were associated with their success rate. Among the 259 patients who successfully completed treatment, 82% (172/209) were regular under GDP and 84% (42/50) were regular under CDP and there was no association between the type of DOT providers and regulatory of treatment ($\div^2$ = 0.01, p = 0.938).

Table 2: Characteristic of tuberculosis patients under Government DPs *vs* Community DPs

Factors	TB Patients under Government DPs			TB Patients under Community DPs		
	Total (N=245) n, (%)	Success rate (N =209) n, (%)	OR , 95% CI	Total (N=58) n, (%)	Success rate (N=50) n, (%)	OR, 95% CI
Sex						
Female	73 (29.8)	66 (90.4)	1.91 (0.75, 5.07)	22 (37.9)	22 (100)	**
Male	172 (70.2)	143 (83.1)		36 (62.1)	28 (77.8)	
Age in years						
≤ 45	154 (62.9)	133 (86.3)	1.25 (0.57, 2.72)	37 (63.8)	34 (91.9)	0.28 (0.05, 1.61)
> 45	91 (37.1)	76 (83.5)		21 (36.2)	16 (76.2)	
Education						
Illiterate	93 (38.0)	78 (83.9)		24 (41.4)	20 (83.3)	
Literate	152 (62.0)	131 (86.2)	1.20 (0.55, 2.60)	34 (58.6)	30 (88.2)	3.54 (0.62, 21.90)
Drug under supervision						
No	157 (64.1)	135 (86.0)	1.16 (0.53, 2.54)	30 (51.7)	23 (76.7)	
Yes	88 (35.9)	74 (84.0)		28 (48.3)	27 (96.4)	8.22 (0.89, 191.20)
Problem under supervision						
No	104 (42.4)	89 (85.6)	1.04 (0.48, 2.20)	33 (56.9)	30 (90.9)	2.50 (0.45, 15.20)
Yes	141 (57.6)	120 (85.1)		25 (43.1)	20 (80.0)	
DP present while taking drugs						
No	176 (71.8)	154 (87.5)	1.78 (0.80, 3.95)	34 (58.6)	27 (79.4)	
Yes	69 (28.2)	55 (79.7)		24 (41.4)	23 (95.8)	5.96 (0.64, 138.68)
Distance						
< 3 km	211 (86.1)	183 (86.7)	2.01 (0.75, 5.25)	52 (89.7)	46 (88.5)	3.83 (0.38, 34.71)
>3 km	34 (13.9)	26 (76.5)		6 (10.3)	4 (66.7)	
Complaining of side-effects						
No	155 (63.3)	137 (88.4)	1.90(0.88, 4.11)	40 (69.0)	34 (85.0)	
Yes	90 (36.7)	72 (80.0)		18 (31.0)	16 (88.8)	1.14 (0.22, 11.46)

** OR was not calculated because of 100% success rate for females

DISCUSSION

The findings of our study revealed that the community volunteers could also be inducted into the programme to work as DPs. The success rate of the patients treated under the supervision of these workers was similar to that of the patients treated by GDPs. These CDPs were found to be reliable and acceptable to the patients. They were also found to be accountable to the health system on par with their counterparts. Similar findings were reported from our centre in an earlier study that the success rates among patients treated by different DOT providers, Anganwadi workers (80%), governmental outreach workers (81%), community volunteers (76%) and Primary Health Institution's staff (76%) were statistically similar[6]. A study from Karnataka[7] observed that the shopkeepers who are from community can be used as DPs because of their accessibility, availability and convenience to the patients. The success rate for TB patients who were treated under shopkeepers continuously was 89.3%, and the success rate for the patients who refused to take treatment under the shopkeepers was 90%. A Bhagyalaxmi *et al* in a study[8] conducted in seven TUs in Ahmedabad Corporation area reported that the available community workers could be involved in supervising the intermittent short course chemotherapy.

A cross-sectional survey[9] conducted in northern Ethiopia among 838 adults (> 15 years' old) demonstrated that among respondents who had prior knowledge of pulmonary tuberculosis (n= 717), 599 (83.5%) accepted the idea of TB treatment by volunteer community members and illiterates, rural residents, married and respondents with a large family size were more likely to support supervised TB treatment using volunteers. The respondents' preferred treatment supervisors were: volunteer community health workers (60%), public health staff (16.5%) and family members (12.7%). Cavalcante *et al* conducted a longitudinal study in a cohort of TB patients in a region of Rio de Janeiro city to compare community-based DOT for TB using community health workers with clinic-based DOT. Treatment success rates for new smear positive and retreatment TB cases were significantly higher among those treated with community based DOT compared to clinic-based DOT[10].

In our study, majority (84%) of the DPs were females demonstrating their dedication and preparedness to work as DPs. Studies from Orissa also reported the similar findings[11,12]. An earlier study[13] from our centre observed that women faced significantly greater TB related stigma and inconvenience than men in terms of inhibitions in discussing illness with others, feeling unwelcome to participate in social events or facing rejection due to their illness. Despite these, women were more likely than men to access health services, get diagnosed and adhere to treatment. Men need additional support for early diagnosis and regular treatment under DOTS. Regularity is another important component for the success of the TB control programme. It is necessary to prevent patients from interrupting treatment throughout the duration of treatment and ensure that the patients receive the right drugs in the right dose for the right duration of treatment. For this, the services of the community workers can also be utilised efficiently in this challenging effort of controlling TB in our country.

The limitations of the study also need to be considered while interpreting the results. The number of CDPs included and interviewed in this study was comparatively lesser than the GDPs. This was because of the limited number of the CDPs available at the time of the study. Moreover, the GDPs had other responsibilities also apart from being the DPs. So, the performance of both GDPs and CDPs was not strictly comparable. The GDPs initiated defaulter action among 70.1% of the patients compared to 44.2% as initiated by CDPs. The corresponding figures reported by the patients were 66% and 67% respectively. DPs mentioned about their overall experience of taking retrieval action when the patients treated under their supervision defaulted. But in the case of the patients, they mentioned about their own DOT providers whether action was initiated or not when they defaulted. There could be variations because DPs mentioned the extent of their overall performance whereas patients mentioned about their own individual DP.

The default rate was less for patients treated by CDP as compared to patients under GDP. However, the performance of the CDPs in terms of success rate was similar to that of the GDPs.

In conclusion, the community volunteers can also be trained and inducted into the programme as DOT providers in order to decentralise and make DOT as friendly as possible to the patients enabling to meet the long term objectives of TB control programme. Also, this study warrants for a larger study including more community volunteers.

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Original Article

KNOWLEDGE AND BEHAVIOUR OF CHEST SYMPTOMATICS IN URBAN SLUM POPULATIONS OF TWO STATES IN INDIA TOWARDS CARE-SEEKING

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Summary

Background: Little information is available on triggers and barriers for seeking appropriate healthcare among chest symptomatics (CS) from slum populations in India.

***Methods*:** Urban slums in Uttar Pradesh (UP) and Karnataka (KA) were selected based on case detection rate (2008), population size and geographic distribution. A door-to-door survey was conducted in 2010 and CS were identified and interviewed. Action taking patterns were collected and factors influencing these among behavers (CS visiting qualified providers) and non-behavers (CS not taking action or resorting to self-medication) compared.

***Results*:** Of 1526 CS in UP and 1515 in KA interviewed, 75% in UP and 58% in KA sought care; of them 79% in UP and 99% in KA visited a qualified provider. More than 80% in both UP and KA underwent recommended tests within a week (mean days: UP-1.8; KA-2.4). Only 16% of respondents in UP and 48% in KA reported that private qualified providers recommended sputum microscopy. Important triggers of visiting a qualified provider were being females; of higher economic status, self-efficacy, suspicion of having TB when suffering from persistent cough and that sputum microscopy should be done to diagnose TB. Additional triggers included knowledge that TB is caused by germs and can affect anyone (UP) and perceptions of quality of care and knowledge that TB is curable (KA).

***Implications*:** There is need to carry out targeted area-specific communication in slums to improve appropriate treatment-seeking behaviour and demand creation for DOTS by CS. The study recommends investments to focus on changing private provider behaviour. **[*Indian J Tuberc 2013; 60:* 95 - 106]**

Key words: Chest symptomatics, Care-seeking behaviour, Tuberculosis, Slums.

BACKGROUND

The Directly Observed Treatment Short-course chemotherapy (DOTS) strategy has been adopted in India for tuberculosis (TB) control and care over a decade ago. Case-finding under the Revised National TB Control Programme (RNTCP) is passive and depends on chest symptomatics (CS) attending health facilities for diagnosis and treatment. Awareness among populations on symptoms of TB and availability of diagnostic and treatment facilities are essential to achieve the objective of universal access for TB care[1]. RNTCP regularly monitors its performance in terms of case detection and treatment outcome. The new smear-positive (NSP) case detection rate (CDR) in 2008 was 68% for India and 67% and 61%[2] in the study states of Uttar Pradesh (UP) and Karnataka (KA) respectively. In order to improve the CDR, RNTCP attempts to improve access by decentralizing public health services, creating awareness through communication and involvement of other healthcare sectors.

There have been several reports on care-seeking behaviour of CS from urban and rural areas[3-6] but very few from urban slums.[7,8] Industrialisation and migration have resulted in rapid population growth with resultant mushrooming of urban slums in India. Slums are generally characterized by overcrowding, low socio-economic status and unhygienic conditions. Its populations are vulnerable to multiple and complex social, economic and medical issues. Higher prevalence of TB has been reported among slum population.[9] Access, availability

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and utilisation of health services and awareness about TB are poor, contributing to increased risk of TB transmission, delayed appropriate health-seeking by CS and complicated internal challenges and barriers to treatment adherence. A nationwide survey on annual risk of TB infection had shown a higher transmission of TB in slums.[10] RNTCP has taken steps to reach all segments of the population through decentralisation and involvement of private providers and communities.[11,12]

The current study, done in November and December, 2010, has attempted to (i) assess knowledge on symptoms of TB among CS, on when to suspect TB and on diagnostic and treatment facilities available, and (ii) relate these to care-seeking behaviour of CS from urban slum populations in study areas.

METHODOLOGY

Study Area

The implementation area for the Market-based Partnerships for Health* (MBPH) TB Control and Care programme comprised 20 districts; seven in UP and 13 in KA. Six of these districts were selected for the study based on NSP CDR (2008) and geographic distribution (Figure 1). Districts of UP were divided into two groups; the most populated town was selected from the high NSP CDR (>100%) group and the town with median population was selected from the low NSP CDR group. In KA, project districts were stratified into three groups and four districts were selected – one with CDR of 40%, two with CDR of 40-70% and one with CDR of more than 70%.

Study Population

Persons aged 18 years or more, reported to have, or having had, persistent cough for two weeks or more during the three months preceding the survey, were interviewed.

Study Design

A cross-sectional community-based survey was conducted. The total sample size was proportionately distributed to the project districts and towns. A three-stage cluster sampling methodology was adopted for selection of CS. In the first stage, project slums were selected using Probability Proportionate to Size from the project towns in each district. The primary sampling unit (PSU) was the selected slum. In the next stage, selected slums were divided into natural clusters; 20% of these were selected using systematic random sampling from each PSU. In the final stage, households were randomly selected from each cluster. In the selected households with more than one CS, one was randomly selected using the *Kish-table* method. In case a CS was not available, a follow-up visit was conducted; a maximum of three revisits were made.

The Sample Size

A sample size of 1500 CS for each state was estimated assuming a change of 5% after the intervention period at 95% confidence and 80% power with a design effect of 1.5. The baseline value was presumed to be 25%.

Definitions

Slum: A compact area of at least 300 people or about 60-70 households of poorly built congested tenements, in unhygienic environment, usually with inadequate infrastructure and lacking in proper sanitary and drinking water facilities.[13]

Chest Symptomatic (CS): A person aged 18 years or more, who reported to have, or having had, persistent cough for two weeks or more during the three months preceding the survey.

Behavers: CS who sought healthcare from a qualified provider.

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* MBPH is a USAID-funded project, implemented from October 2008 to May 2012 by Abt Associates India Pvt. Ltd. It is a highly innovative project that aimed to test commercially viable models, engage the private sector, and use private sector resources for delivering public health services to urban and rural base of the Pyramid populations.

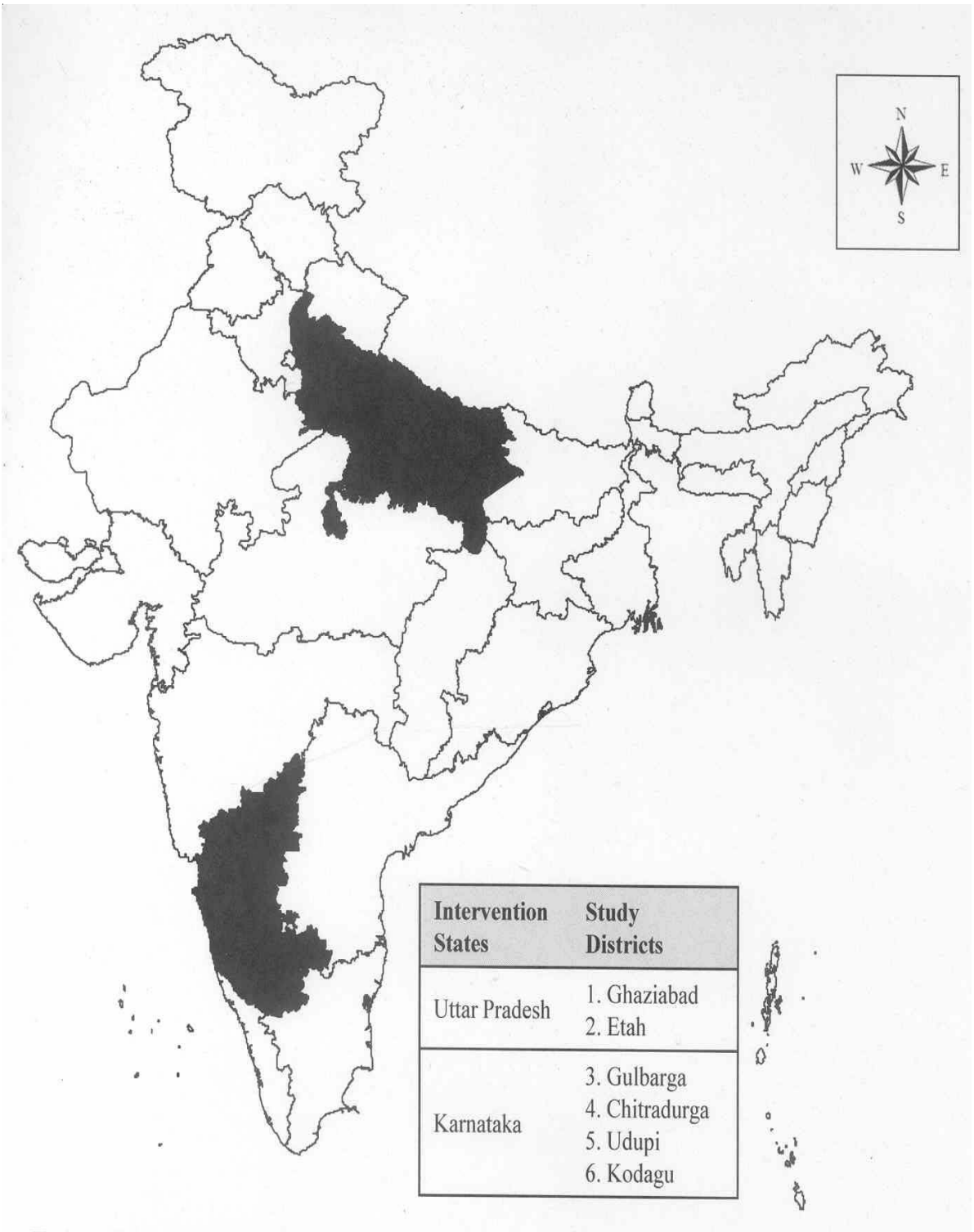

Figure 1: Program Area Map

Non-behavers: CS who did not take any action or resorted to self-medication.

Qualified Provider: A person legally qualified to practise modern medicine in India and holds an MBBS, or equivalent, degree (allopathic provider).

Practitioner of Indigenous Systems of Medicine and Homeopathy (ISMH): A person who may legally practise an alternative system of medicine in India. This includes practitioners of ayurveda, siddha, unani and homeopathy and therapies such as yoga and naturopathy[14] *(AYUSH).*

Less Than Fully Qualified (LTFQ) Provider: A healthcare provider who is seen and accepted as such by members of his/her local community, but who does not have a legally recognized qualification to practise any form of medicine in India.

Tools for Data Collection

A pre-coded, semi-structured interview schedule was used. This included demographic and socio-economic characteristics of respondents, their care-seeking pattern when suffering from persistent cough, and reasons for choice of provider. In addition, multi-items with *Likert* scale response to measure the respondents' knowledge, attitude and beliefs (KAB) on TB were used. The questionnaire was translated to local languages and pre-tested before finalisation. Responses to open-ended questions were translated and coded appropriately.

Data Management

An experienced, field team from Indian Market Research Bureau (IMRB) conducted face-to-face interviews in private settings. Field supervisors carried out back-checks and spot-checks for listing and interviews to monitor quality of field work. Data was double-entered to ensure data quality.

Statistical Analysis

Data was analysed using PASW Statistics 18.0 version (IBM, New York, USA). Chi square test was used to measure statistical significance between proportions. In addition, multivariate logistic regression was used to identify triggers and barriers for desired behaviour. The results are presented as per cent, adjusted proportions, odds ratios and mean score *(Likert scales)* with statistical significance level at p-value ≤ 0.05. Sampling weights were applied prior to analysis to address the unequal probability of selection of research districts, slums and CS.

Ethics Approval

The study was approved by the Institutional Ethics Committee of Abt Associates Inc. Pvt. Ltd. Respondents were informed in their mother-tongue about the purpose of the study and assured of confidentiality of data and right to withdraw from the study at any time. An oral informed consent was obtained from participants.

RESULTS

A total of 11,699 families in UP and 9,489 families in KA, covering a population of 68,324 in UP and 49,279 in KA were interviewed. The prevalence of CS in slums was 2.2% and 3.2% in UP and KA respectively.

Socio-demographic Profile of Study Subjects

Table-1 shows the socio-demographic profile of 1,526 CS interviewed in UP and 1,515 in KA. In the slums of UP, 53% were below 45 years and 10% above 65 years; 54% male; 25% had a family size of five or more; 55% illiterate; 44% unemployed and 54% belonged to low Socio-economic Class (SEC). In KA, 43% were below 45 years and 17% above 65 years; 53% male; 22% had a family size of five or more; 50% illiterate; 40% unemployed and 62% belonged to low SEC. In UP, 53% were Hindu and 47% Muslim while in KA 81% were Hindu.

Care-seeking Pattern

Figure-2 shows that in UP, 1,145 (75%) of the 1,526 CS interviewed visited healthcare

Table 1: Socio-demographic characteristics of chest symptomatics in urban slum populations, Uttar Pradesh and Karnataka, 2010

	Uttar Pradesh	Karnataka
	No (%)	No (%)
Age in years		
≤45	813 (53)	658 (43)
46-65	567 (37)	600 (40)
>65	146 (10)	257 (17)
Sex		
Female	699 (46)	719 (47)
Male	827 (54)	796 (53)
Family size		
1-2	644 (42)	445 (29)
3-4	500 (33)	733 (48)
5+	382 (25)	337 (22)
Education		
Illiterate	838 (55)	756 (50)
Below primary	124 (8)	210 (14)
Primary & Middle	324 (23)	339 (22)
Secondary & above	240 (16)	210 (14)
Occupation		
Unemployed	672 (44)	590 (40)
Unskilled workers	415 (27)	646 (43)
Skilled workers	439 (29)	279 (18)
Socio economic class		
Low (SEC E)	824 (54)	943 (62)
Medium (SEC C & D)	565 (37)	440 (29)
High (SEC A & B)	136 (9)	132 (9)
Marital Status		
Never married	168 (11)	135 (9)
Currently married	1158 (76)	1153 (76)
Widow/ widower/ separated/ divorced	199 (13)	227 (15)
Religion		
Hindu	802 (53)	1233 (81)
Muslims	716 (47)	266 (18)
Others	7 (0.5)	16 (1)
Caste		
SC/ST	507 (33)	771 (51)
Other Backward Caste	741 (47)	661 (44)
Others	176 (11)	29 (2)
No response/ DK	101 (7)	54 (4)
N	1526	1515

providers as a first action; 53% went to qualified private providers, 26% to public sector providers, 15% to LTFQ providers and the remaining to pharmacies (4%) or ISMH (2%). In KA, 879 (58%) of 1,515 CS interviewed visited a healthcare provider as a first action; 55% to qualified private providers, 44% to public sector providers and the remaining to LTFQ providers (0.2%), ISMH (0.5%) or pharmacies (0.1%). More than 50% of subjects approached private providers first in both KA and UP, irrespective of the level of education, employment or socio-economic status (data not tabulated).

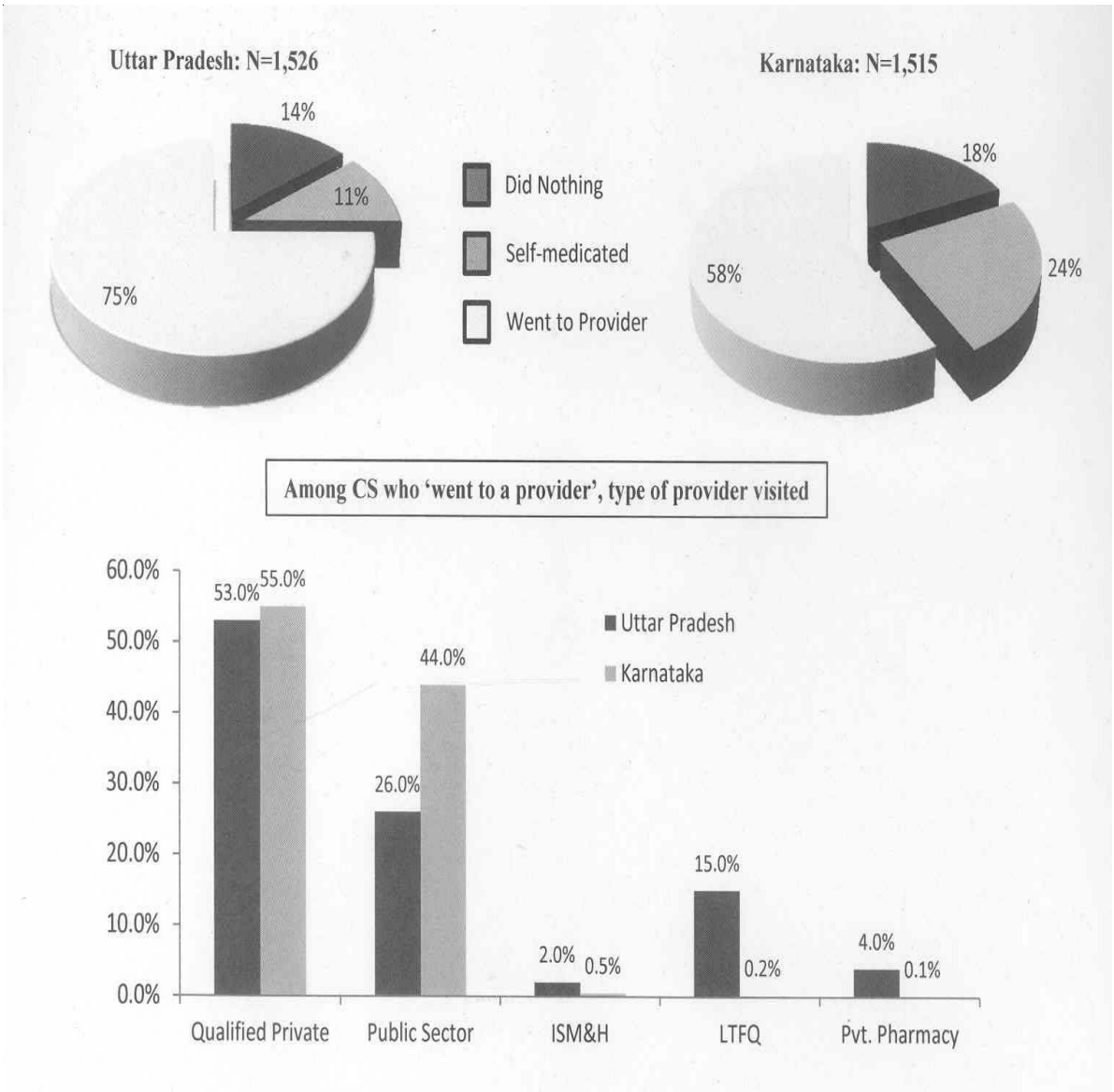

Figure 2: Care-seeking pattern of chest symptomatics among slum populations, Uttar Pradesh and Karnataka, 2010

Table-2 shows the reasons for choice of provider. In UP, these were 'good reputation' (68% private, 57% public), 'trust-worthy' (43% private, 20% public), 'not costly' (36% private, 75% public) and easy access (37% private, 28% public). In KA, these were 'good reputation' (55% private, 46% public), 'treated friendly' (64% private, 37% public), 'not costly' (24% private, 63% public) and easy access (27% private, 16% public). Many CS, 381 (25%) in UP and 636 (42%) in KA, did not visit a provider. Of them, 11% (UP) and 24% (KA) resorted to self- medication. The key reasons for not visiting a provider (Table-3) were 'lack of money' (51% in UP and 46% in KA) and 'symptoms not severe' (41% in UP and 30% in KA).

Table 2: Reasons for choice of provider among CS in urban slum populations, Uttar Pradesh and Karnataka, 2010

Reason	Uttar Pradesh			Karnataka	
	Public	**Private qualified**	**LTFQ**	**Public**	**Private qualified**
	No (%)	**No (%)**	**No (%)**	**No (%)**	**No (%)**
Good reputation	171 (56.5)	413 (68.4)	71 (42.3)	176 (45.6)	265 (55.0)
Not costly	227 (75.1)	219 (36.3)	106 (63.5)	242 (62.9)	113 (23.6)
Close to home/easy access	85 (28.1)	224 (37.1)	93 (56.0)	61 (15.9)	130 (27.0)
Treated friendly	52 (17.4)	141 (23.3)	16 (9.3)	143 (37.1)	307 (63.9)
Trust worthy	61 (20.3)	262 (43.4)	57 (34.3)	15 (3.9)	29 (6.0)
Friend/Relatives recommended	24 (7.8)	79 (13.2)	8 (4.9)	71 (18.4)	47 (9.7)
N	302	604	167	385	481

Table 3: Reasons for not visiting a provider among chest symptomatics in urban slum populations, Uttar Pradesh and Karnataka, 2010

Reasons	**Uttar Pradesh (N=381)**	**Karnataka (N=636)**
	No (%)	**No (%)**
Lack of money	194 (51)	295 (46)
Symptoms not severe	156 (41)	195 (30)
Pressure at work	37 (10)	193 (30)
Domestic preoccupation	41 (11)	12 (2)
Lack of transport	9 (2)	12 (2)
Dissatisfaction	74 (19)	50 (8)
Could treat themselves	74 (19)	55 (9)
Felt better before seeking help	16 (4)	39 (6)
Do not know	2 (0.4)	17 (3)

Factors Influencing Care-seeking Behaviour

Table-4 shows the socio-economic factors influencing desired behaviour using adjusted odds ratio (AOR). In UP and KA, being male (AOR 0.57; 0.69), greater number of adults in the family (AOR 2.84; 1.51), and higher socio-economic status (AOR 2.24; 1.50) were found to be significantly associated with the desired behaviour.

Table-5 shows the influence of knowledge, attitude and beliefs about TB on desired behaviour. In UP, knowledge that TB is caused by germs (AOR 5.89), suspecting TB for persistent cough (AOR

Table 4: Influence of socio-economic factors on care-seeking among chest symptomatics in urban slum populations, Uttar Pradesh and Karnataka, 2010

	UTTARPRADESH (1288)				**KARNATAKA (1506)**			
	Total	**Behavers (906)**			**Total**	**Behavers (866)**		
		No	**%**	**AOR (95% CI)**		**No**	**%**	**AOR (95% CI)**
Age (≤45)	581	391	67		544	279	51	
46-65	492	358	73	1.25 (0.90-1.75)	565	327	58	1.07 (0.72-1.61)
>65	215	157	73	1.08 (0.82-1.42)	397	260	65	1.25 (0.94-1.66)
Sex (Female)	584	444	76		678	423	62	
Male	704	462	66	0.57 (0.42-0.79)*	828	443	53	0.69 (0.48-0.99)*
Adults (≤3)	483	294	61		418	196	47	
4-5	441	305	69	0.83 (0.59-1.17)	732	462	63	1.51 (1.05-2.18)*
5+	364	306	84	2.84 (1.90-4.23)*	357	209	59	1.15 (0.75-1.78)
Education (Illiterate)	625	456	73		516	223	43	
Below primary	96	62	64	0.77 (0.46-1.33)	223	154	69	1.49 (0.85-2.61)
Primary & Middle	306	206	67	0.87 (0.61-1.23)	446	289	65	0.79 (0.51-1.23)
Secondary & Above	262	183	70	0.93 (0.61-1.42)	321	199	62	1.43 (0.84-2.44)
Occupation (Unemployed)	608	447	73		576	334	58	
Unskilled workers	300	201	67	0.92 (0.63-1.35)	587	358	61	1.18 (0.71-1.95)
Skilled worker	379	258	68	0.77 (0.54-1.09)	344	174	51	0.81 (0.46-1.43)
Socioeconomic class (Low)	633	439	69		823	444	54	
Medium	521	360	69	0.79 (0.58-1.09)	517	316	61	1.50 (1.01-2.24)*
High	134	108	80	2.24 (1.16-4.33)*	166	106	64	1.58 (0.85-2.93)

* Significantly at $p \leq 0.0$

5.36) and self-efficacy (AOR 1.89) were the main triggers for desired behaviour. In KA, perceived quality of care (AOR 2.99), knowing that sputum microscopy is a test for diagnosis of TB (AOR 2.40), suspecting TB for persistent cough (AOR 1.81) and self-efficacy (AOR 1.84) were key triggers for desired behaviour.

Action taken by provider as reported by chest Symptomatics

CS reported that investigations were ordered for 34% of those who visited public sector providers and for 37% visiting private qualified providers in UP. In KA, the corresponding proportions were 33%

Table 5: Influence of knowledge, attitude and belief on care-seeking among chest symptomatics in urban slum populations, Uttar Pradesh and Karnataka, 2010

Knowledge, Attitude & Beliefs about TB	Uttar Pradesh					Karnataka				
	Behaver (906)		Non-Behaver (382)		AOR (95% CI)	Behaver (866)		Non-Behaver (640)		AOR (95% CI)
	No	%	No	%		No	%	No	%	
Caused by germs	861	95	301	79	5.89 (3.48-9.95)*	665	77	470	73	1.16 (0.74-1.82)
Confirmed by sputum test	751	83	325	85	0.56 (0.33-1.12)	409	47	244	38	1.53 (1.05-2.23)*
Infected through air	833	92	370	97	0.41 (0.21-1.09)	665	77	433	68	1.67 (1.09-2.55)*
Curable	840	93	357	94	0.74 (0.38- 1.44)	566	65	353	55	1.65 (1.12-2.43)*
Sputum test as a test for diagnosis	875	97	355	93	2.11 (0.97-4.59)	684	79	410	64	2.40 (1.54-3.75)*
Suspected TB: Had persistent cough	81	9	4	1.2	5.36 (1.89-15.18)*	52	6	13	2	1.81 (1.13-3.46)*
	No	Mean score	No	Mean score		No	Mean score	No	Mean score	
It can affect anybody	906	3.65	382	3.52	1.27 (1.09-1.47)*	866	3.59	640	3.6	0.96 (0.75-1.23)
Doesn't infect by sharing/talking/ having sex with TB person	906	1.59	382	1.44	1.42 (1.16-1.75)*	866	2.65	640	2.69	0.90 (0.70-1.15)
Cannot confirm by blood test	906	3.47	382	3.04	1.19 (1.09-1.29)*	866	2.11	640	2.07	1.00 (0.77-1.31)
Perceived quality of care	906	4.76	382	4.79	0.94 (0.66-1.34)	866	4.18	640	3.91	2.99 (2.06-4.40)*
Self-efficacy	906	4.81	382	4.67	1.89 (1.33-2.67)*	866	4.04	640	3.82	1.84 (1.38-2.46)*
TB is life threatening	906	4.49	382	4.44	1.05 (0.83-1.32)	866	3.5	640	3.73	0.65 (0.51-0.84)*

* Significantly at $p \leq 0.0$

Table 6: Action taken by provider as reported by chest symptomatics in urban slum populations, Uttar Pradesh and Karnataka, 2010

	Uttar Pradesh			Karnataka	
	Public	Private		Public	Private
	(N=302)	Qualified (N=604)	LTFQ (N=167)	(N=385)	Qualified (N=481)
	No (%)	No (%)		No (%)	No (%)
Advised investigations	24 (8)	75 (12)	14 (8)	26 (7)	26 (5)
Advised investigations & medicines	78 (26)	150 (25)[a]	14 (8)*	100 (26)	109 (23)
Investigations recommended	102 (34)	225 (37)	28 (17)	126 (33)	135 (28)
Sputum	34 (36)[a]	37 (16)	8 (25)	71 (61)[a]	69 (48)
X-ray	54 (58)	129 (57)	18 (56)	89 (77)	113 (78)
CT scan	2 (2)	0.45 (0.2)	0.45 (1)	12 (10)	23 (16)
Blood test	60 (64)	148 (66)	19 (60)	56 (48)	75 (52)
Urine test	4 (4)	12 (5)	3 (11)	45 (39)	53 (37)
Prescribed Medicines	199 (66)	375 (62)[a]	138 (83)	241 (63)	330 (67)
Refer to other provider	-	4 (0.7)	1 (0.5)	7 (2)	11 (2)
Refer to DMC	1 (0.4)	-	-	3 (1)	4 (1)
None of these	-	-	-	8 (2)[a]	1 (0.2)

** Significantly different from the LTFQ ($p \leq 0.05$); [a] significantly different from the next proportion ($p \leq 0.05$)*

and 28% (Table 6). Of the investigations ordered, X-rays and blood tests were reportedly common. In UP, 58% and 57% reported that X-rays were ordered by public and private qualified providers respectively. In KA, proportions were 77% and 78%. The percentage reporting ordering of blood tests by public sector and private qualified providers were 64% and 66% in UP and 48% and 52% in KA. Sputum microscopy was reportedly ordered for 36% (UP) and 61% (KA) by public sector providers and 16% (UP) and 48% (KA) by private qualified providers. In UP, 85% and in KA, 82%, reported that the recommended tests were carried out within one-seven days (mean days - 1.8 in UP and 2.4 in KA) (data not tabulated).

DISCUSSION

After more than a decade of RNTCP implementation, the salient finding, from this large-scale, community-based, study to assess care-seeking behaviour of CS among urban slum populations, is that 25% in UP and 42% in KA did not seek healthcare. However, among CS who sought care, most visited the right type of providers.

We observed that a good proportion of CS did not take desired action, though they had the required knowledge on TB, showing that knowledge alone is not adequate to translate into desired behaviour. The main barrier for not taking desired action was lack of self-efficacy and being male. The study also confirms earlier findings from a rural and urban area that financial problems, symptoms not being considered severe and pressure of work were the main reasons for not visiting providers.[15] This needs attention from policy makers on how to reach the poor and on carrying out targeted and localized communication to increase treatment-seeking behaviour. Existing ACSM[16] efforts under RNTCP need to be strengthened and messages should be area and population specific.

The study has identified that, in UP, 'suspicion of TB' when the respondent noted persistent cough and 'knowledge that TB is caused by germs' were the main triggers for desired behaviour (AOR: 5.36 and 5.89). In KA, the main triggers were positive perception of 'quality of care' and knowledge that sputum microscopy is the test for diagnosis (AOR 2.99 and 2.40). Communication strategies should use this information to promote desired behaviour among CS and enable early diagnosis and treatment.

Another important finding from this study is that, among behavers, more than half (56% in UP and 55% in KA) first visited a private provider. In both states, the principal reason for selecting a public sector provider was cost and that for the private provider was proximity and the belief that they are treating the patient 'nicely'. RNTCP has several schemes for involvement of NGOs and private providers.[17] This highlights the need for concerted efforts to prioritize private sector engagement by RNTCP for early diagnosis and treatment.

The study has observed that 15% of CS in UP approach LTFQ providers for healthcare. To the extent that is legally possible, they can be engaged by RNTCP for referral of CS to nearby Designated Microscopy Centers (DMC) for diagnosis and treatment initiation. Consumer confidence in LTFQ providers indicates that they may be acceptable as community DOT providers for TB patients. Opinion leaders and key influencers may be mobilized to help improve awareness on TB in the community and generate demand for DOTS.

More than 60% reported that medicines were prescribed without investigations in both UP and KA. X-rays and blood tests, rather than sputum microscopy, are the commonly recommended tests by both public and private qualified providers. Another study from Bangalore slums had also shown that sputum microscopy was ordered only for 16% while X-rays for 48%.[8] CS in both states reported that the recommended tests were carried out with little delay. This survey suggests that private providers should be educated on the need to suspect TB when presented with a CS. They should also be provided with evidence to support sputum examination for diagnosis of TB.

Limitations

The limitations of our study are possible interviewer-bias and recall-bias on the part of respondents with regard to the type of symptoms, care-seeking and type of healthcare providers consulted. However, this bias would be equally applicable for all groups studied. Findings of the study may only apply to slum areas with similar socio-demographic characteristics.

The strength of this study is that data was obtained from a considerable number of CS in slums of two different states several years into the implementation of RNTCP. These findings could serve as a base for subsequent studies and possible interventions.

Policy Implications

There is need for area-specific ACSM interventions with special reference to slums to enable universal access to TB diagnosis and care. Urgent action is required to strengthen private provider engagement to address TB among slum populations. Promotional activities on availability of good quality diagnostic and treatment facilities for TB in both public and private

healthcare facilities need to be disseminated widely to vulnerable populations after capacity building of the latter group. In addition, the findings of this study recommend investments to focus on changing provider behaviour.

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Original Article

CLINICAL FORMS AND DETERMINANTS OF DIFFERENT LOCATIONS OF EXTRA-PULMONARY TUBERCULOSIS IN AN AFRICAN COUNTRY

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Summary

***Background*:** Extra-pulmonary tuberculosis (EPTB) accounts for about 15% to 36% of all cases of TB and its prevalence has significantly increased with the advent of the global pandemic of human immune-deficiency virus (HIV) infection. A few studies are available on the determinants of EPTB.

***Aims*:** To determine the distribution and determinants of the main locations of EPTB in the context of high endemicity for HIV infection.

***Methods*:** This was a cross-sectional study among patients aged ≥15 years, receiving care in the pneumology service of the Yaounde Jamot Hospital, between October 2010 and December 2011. Logistic regressions were used to investigate potential determinants of different locations of EPTB.

***Results*:** Of the 788 eligible patients admitted during the study period, 100 (12.7%) had isolated EPTB, and 158 (20.1%) had both PTB and EPTB. Among 258 patients definitively included, 162 (62.8%) were men and the median age was 33 (25.75-44) years. Frequent extra-pulmonary locations of tuberculosis were lymph nodes (126 patients, 48.3%), pleura (121 patients, 46.4%) and peritoneum (25 patients, 9.6%). Using isolated pleural TB as a referent, independent determinants of isolated lymph node tuberculosis were HIV infection [odds ratio (95% CI), 2.58 (1.25-5.32)], duration of symptoms >6 weeks [2.41 (1.11-5.22)] and pulmonary involvement [2.39 (1.14-5.05)]. HIV infection [2.23 (1.06- 4.70)] and duration of symptoms >6 weeks [2.31 (1.08-4.96)] were also independent determinants of multifocal/disseminated tuberculosis.

Conclusion: EPTB with or without concomitant PTB is frequent in this setting, with HIV infection being the main determinant. **[*Indian J Tuberc 2013; 60:* 107 - 113]**

***Key words*:** Tuberculosis sites, Risk factors, HIV infection, Cameroon

INTRODUCTION

Tuberculosis (TB) remains a major public health problem in spite of the control strategies implemented over time [1]. EPTB accounts for about 15% to 36% of all cases of TB and its prevalence has significantly increased with the advent of the global pandemic of human immune-deficiency virus (HIV) infection[2, 3]. Studies on TB have focused more on pulmonary TB, the most frequent form of the disease [1], and the starting site for the dissemination of the infection to other organs. Indeed, virtually all organs can be affected by TB infection. Common EPTB sites include pleura, lymph node, bones and joints[2, 4]. Other forms of EPTB such as neuro-meningeal or miliary TB are less frequent but are associated with worse outcomes[5-7]. In sub-Saharan Africa where the highest global population of individuals with HIV infection is found, EPTB is highly associated with HIV infection[3, 8, 9]. In general, however, the determinants of different locations of EPTB have not been appropriately investigated. In a recent retrospective study conducted in the USA [10], it was found that the risk of neuro-meningeal or disseminated TB was higher in patients with HIV infection, but much higher in those with CD4 counts lower than 100/mm^3. In the same study [10], patients with neuro-meningeal TB were less likely to have concomitant pulmonary involvement as opposed to their counterparts with lymph node TB. The aim of this study was to investigate the main EPTB sites and their determinants, with a major concentration on HIV infection in a low-resource setting with high endemicity for both tuberculosis and HIV infection.

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MATERIAL AND METHODS

Study setting and participants

This cross-sectional study was conducted in the pneumology service of the Yaounde Jamot Hospital (YJH) over a period of 15 months from October 2010 to December 2011. The study setting has been described in detail elsewhere[11]. In brief, the YJH is referral hospital for tuberculosis and chest diseases for the capital city of Cameroon (Yaounde) and surrounding areas, and is one of the major centres for diagnosis and treatment (CDT) of tuberculosis in the country. All patients aged 15 years and above hospitalised at the chest unit of YJH for TB during the study period were considered for inclusion in this study.

Detection, definitions and classification of tuberculosis cases

All patients receiving care for TB were seen by a physician, and those with extrapulmonary involvement were systematically seen by one of the seven chest specialist physicians. Investigation for extra-pulmonary involvements is an integral part of the routine workup of patients with tuberculosis in this service, and chest X-ray is systematically requested for all patients with EPTB.

Three direct sputum examinations were systematically performed for all patients who could produce a sputum sample, as well as a standard chest X-ray. The diagnosis of EPTB was based on radiological examinations; bacteriological, cytological, biochemical and histological examinations of fluids or pathological tissue samples collected from the involved organs; or strong clinical evidence consistent with active EPTB, followed by a decision of a clinician to treat with a full course of anti-tuberculosis chemotherapy. Patients who received a final diagnosis of tuberculosis were also screened for HIV infection after informed consent as previously described [11]. This included detection of anti-HIV 1 and anti-HIV 2 antibodies in the serum with the use of two rapid tests: the Determine HIV ½ test (Abbot Laboratories, Tokyo, Japan) and the Immunocomb II HIV 1 and 2 Bispot kit (Organics, Courbevoie, France). A patient was classified as HIV positive when the two tests were positive. For discordant tests, a confirmatory Western blot test (New Lav lot; Sanofi Diagnostics Pasteur, Chaska, Minnesota, SA) was conducted.

The following international definitions were applied in the service at the time of the study[12,13]: 1) smear-positive pulmonary tuberculosis (SPTB+): acid-fast bacilli (AFB) found in at least two sputum specimens; 2) smear-negative pulmonary tuberculosis (SPTB-): persisting negativity on three sputum examinations after a ten-day course of non-specific antibiotic treatment in a patient with tuberculosis-like clinical and radiological signs, and in the absence of any obvious cause; 3) EPTB - tuberculosis involving organs other than lungs, for instance pleura, lymph node, abdomen, genito-urinary system, skin, joints and bones, meninges, etc. A patient was classified as a new case (first episode of tuberculosis) if he had never been exposed to anti-tuberculosis treatment for more than one month in the past.

Procedures

All patients hospitalised in the service for TB were prospectively included in the study. Upon admission, all patients received a clinical examination including data collection on functional signs (general, pulmonary and extra-pulmonary) and physical signs relating to pulmonary and extra-pulmonary TB.

Socio-demographic data collected included age, sex, residence (urban *vs* rural) and formal level of education. Past medical history data included current smoking (yes *vs* no), alcohol consumption (yes *vs* no), vaccination with BCG and co-morbidities (diabetes mellitus). Clinical details included: cough, expectoration, haemoptysis, chest pain, asthenia, anorexia, fever, weight loss and body mass index. Radiographic data were collected on the lungs' involvement, the presence of pleural effusion, mediastinal or hilar lymph node. Biological data included the results of the HIV test, full blood count, and CD4 count (for HIV positive patients only). The study was approved by the administrative authorities of the YJH and Cameroon National Ethics Committee.

Statistical methods

Data were analysed with the use of the SPSS® software version 17 for Windows (SPSS Inc., Chicago, USA). Results are expressed as mean and standard deviation, median (25-75th percentiles) and count (percentage). Group comparisons used χ^2 or Fischer exact test for qualitative variables and Student t test or non-parametric equivalent for quantitative variables. Multinomial logistic regressions models were used to investigate potential determinants of extra-pulmonary location of TB. Potential candidate predictors were first investigated in univariable analysis. Significant variables (based on a threshold probability <0.1) were entered all together in the same multivariable model. A p-value <0.05 was used to characterise statistically significant results.

RESULTS

Study population

A total of 788 patients with TB were hospitalised in the service during the study period, of whom 530 (67.3%) had isolated PTB, 100 (12.7%) had isolated EPTB, and 158 (20.1%) had both PTB and EPTB. Overall, 258 (32.8%) patients had EPTB with or without pulmonary TB and were definitively included in this analytic sample. Their demographic, clinical and paraclinical features are detailed in Table 1. Of the 258 patients included, 162 (62.8%) were men and their median age (25th -75th percentiles) was 33 (25.75-44) years. HIV-1 test was positive in 133 (51.6%) patients. The prevalence of HIV infection was 42% and 57.6% respectively among patients with EPTB and PTB/EPTB (p< 0.0001). The median (25th - 75th percentiles) duration of symptoms before consultation was 12 (6-20) weeks. One hundred and fifty eight (61.2%) patients had associated pulmonary TB and 121 (46.9%) had anaemia (haemoglobin level <10g/dl).

Clinical forms of extra-pulmonary tuberculosis

The clinical forms of EPTB are depicted in Figure 1. Lymph node TB was the most frequent (126 patients, 48.3%) followed by pleural TB (121 patients, 46.4%) and peritoneal TB (25 patients, 9.6%). Among the 126 patients with lymph node TB, 61 (48.4%) had isolated extra-thoracic lymph node TB, 53 (42.1%) had isolated intra-thoracic lymph node TB and 12 (9.5%) had both extra- and intra-thoracic lymph node TB. Of the 12 patients who had ostéo-articular TB, nine (75%) had Pott's disease, two (16.7%) had knee TB and one (8.3%) had hip TB.

Profile of participants by clinical forms of extra-pulmonary tuberculosis

Of 258 patients with EPTB, 85 (32.9%) had isolated lymph node TB, 77 (29.8%) had isolated pleural TB, 75 (29.1%) had multifocal or disseminated TB and 21 (8.1%) had other isolated extra-pulmonary localization (other single focal EPTB). The main characteristics of patients with EPTB by site are presented in Table 1. No significant difference by clinical form was found for demographic characteristics and distribution of general clinical signs. The prevalence of HIV infection was higher in patients with isolated lymph node TB (61.2%) and those with multifocal/disseminated TB (61.3%) compared to patients with isolated pleural TB (37.7%) or other isolated extra-pulmonary involvement (28.6%) (p = 0.001). There was a borderline significant difference by site in the median duration of symptoms prior to the consultation (p=0.046), while the median CD4 count was similar among those with HIV infection across sites (p=0.87). Pulmonary involvement was found in 66 (77.6%) patients with isolated lymph node TB, 42 (54.5%) patients with isolated pleural TB, 44 (58.7%) patients with multifocal/disseminated TB and six (28.6%) patients with other isolated extra-pulmonary localization (p <0.001). The prevalence of anaemia also significantly varied by site (p=0.08).

Independent risk factors for extra-pulmonary tuberculosis locations

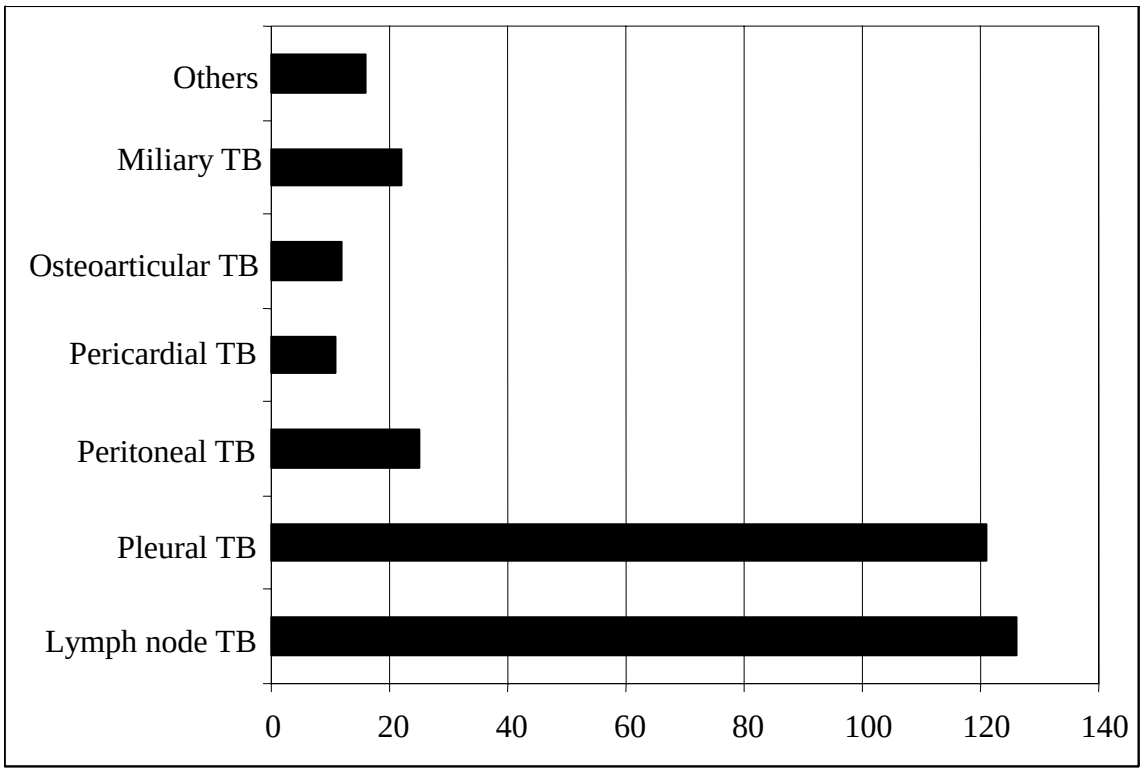
In multinomial logistic regression analysis, and using 'isolated pleural TB' as a referent, independent determinants of isolated lymph node TB were HIV infection [odds ratio (95% confidence interval) 2.58 (1.25-5.32)], duration of symptoms >

6 weeks [2.41 (1.11-5.22) and pulmonary involvement [2.39 (1.14-5.05)]. HIV infection [2.23 (1.06- 4.70)] and duration of symptoms > 6 weeks [2.31(1.08-4.96)] were also associated with multifocal/disseminated TB. Other isolated EPTB involvements were less frequently [0.28 (0.09-0.90)] associated with pulmonary TB than pleural tuberculosis (Table 2).

Table 1: Demographic, clinical and selected paraclinical features of 258 patients with extrapulmonary tuberculosis by site

Characteristics	Total	Clinical forms of extrapulmonary TB				P value
		Isolated lymph node TB	Isolated pleural TB	Multifocal/ Disseminated TB	Other single focal TB	
N (%)	258	85 (32.9%)	77 (29.8)	75 (29.1)	21 (8.1%)	
Age, years						
Median (IQR)	33 (25.75-44)	34 (26-46.5)	34 (24.5-41.5)	33 (28-45)	29 (21.5-33.5)	0.098
< 33	124 (48.1)	35 (41.2)	37(48.1)	37 (49.3)	15 (71.4)	0.100
Men, n (%)	162 (62.8)	48 (56.5)	53 (68.8)	47 (62.7)	14 (66.7)	0.425
Urban residency, n (%)	216 (83.7)	13 (15.3)	12 (15.6)	14 (18.7)	3 (14.3)	0.927
Formal education						
Secondary , n (%)	206 (79.8)	70 (82.4)	61 (79.2)	59 (78.7)	16 (76.2)	0.899
University, n (%)	52 (20.2)	15 (17.6)	16 (20.8)	16 (21.3)	5 (23.8)	
Smoking, n (%)	38 (14.7)	9 (10.6)	10 (13.0)	15 (20.0)	4 (19.0)	0.345
Alcohol use, n (%)	66 (25.6)	19 (22.4)	18 (23.4)	22 (29.3)	7 (33.3)	0.598
BCG, n (%)	200 (77.5)	64 (75.3)	59 (76.6)	59 (78.7)	18 (85.7)	0.767
Diabetes, n (%)	2 (0.8)	1 (1.2)	0 (0)	1 (1.2)	0 (0)	0.742
HIV infection, n (%)	133 (51.6)	52 (61.2)	29 (37.7)	46 (61.3)	6 (28.6)	**0.001**
History of TB, n (%)	18 (7.0)	7 (8.2)	6 (7.8)	4 (5.3)	1 (4.8)	0.860
Anorexia, n (%)	178 (69.0)	65 (76.5)	47 (61.0)	53 (70.7)	13 (61.9)	0.165
Asthenia, n (%)	205 (79.5)	72 (84.7)	56 (72.7)	61 (81.3)	16 (76.2)	0.276
Weight loss, n (%)	236 (91.5)	79 (92.9)	69 (89.6)	69 (92.0)	19 (90.5)	0.889
Fever, n (%)	225 (87.2)	78 (91.8)	65 (84.4)	64 (85.3)	18 (85.7)	0.494
Symptoms duration						
Median (IQR), weeks	12 (6-20)	14 (8-24)	10 (5-16)	12 (8-20)	12 (7-18)	**0.046**
≤ 6 weeks, n (%)	66 (25.6)	17 (20.0)	29 (37.7)	15 (20.0)	5 (23.8)	**0.036**
BMI, kg/mm²						
Median(IQR)	19.8 (18.2-22.0)	19.3 (17.9-21.6)	20.1 (18.7-33.5)	19.9 (18.5-21.7)	19.1 (17.4-22.1)	0.395
< 18.5	74 (28.7)	29 (34.1)	18 (23.4)	18 (24.0)	9 (42.9)	0.161
Pulmonary TB, n (%)	158 (61.2)	66 (77.6)	42 (54.5)	44 (58.7)	6 (28.6)	**< 0.001**
Hb < 10 g/dl, n (%)	121 (46.9)	49 (57.6)	27 (35.1)	39 (52.0)	6 (28.6)	**0.008**
Leukocyte counts						
< 4000/mm^3, n (%)	45 (17.4)	13 (15.3)	11 (14.3)	16 (21.3)	5 (23.8)	0.535
≥ 4000/mm^3, n (%)	213 (82.6)	72 (84.7)	66 (85.7)	59 (78.7)	16 (76.2)	
Lymphocytes count						
< 1500/mm^3, n (%)	110 (42.6)	41 (48.2)	29 (37.7)	36 (48.0)	4 (19.0)	**0.057**
≥ 1500/mm^3, n (%)	148 (57.4)	44 (51.8)	48 (62.3)	39 (52.0)	17 (81.0)	
Median CD4(IQR), £ /mm^3	118 (48-259.8)	84 (39.5-192.0)	133 (44.8-276.5)	156 (67-296)	186.5 (3-445.5)	0.871

TB - tuberculosis; HIV- Human Immunodeficiency Virus; IQR - interquartile range; BMI - body mass index; Hb - haemoglobin level;
£, only for HIV positive patients



TB - tuberculosis

Figure 1: Clinical forms of extrapulmonary tuberculosis among 258 patients with extrapulmonary involvement

Table 2: Odds ratios and 95% confidence intervals for independent determinants of major extrapulmonary tuberculosis sites with using pleural tuberculosis as a referent

Variable	Lymph node TB *vs* Pleural TB		Multifocal/Disseminated TB *vs* Pleural TB		Other focal TB *vs* Pleural TB	
	AOR(95%CI)	**p value**	**AOR(95%CI)**	**p value**	**AOR(95%CI)**	**p value**
HIV infection	**2.58 (1.25-5.32)**	**0.011**	**2.23 (1.06-4.70)**	**0.034**	0.91 (0.26-3.15)	0.884
Symptoms duration > 6 weeks	**2.41 (1.11-5.22)**	**0.025**	**2.31 (1.08-4.96)**	**0.031**	2.29 (0.71-7.33)	0.165
Pulmonary involvement	**2.39 (1.14-5.05)**	**0.022**	0.75 (0.36-1.55)	0.432	**0.28 (0.09-0.90)**	**0.032**
Haemoglobin level < 10 g/dl	0.63 (0.31-1.28)	0.198	0.62 (0.29-1.30)	0.203	0.72 (0.20-2.57)	0.607
Lymphocytes count< 1500/mm^3	0.874 (0.43-1.79)	0.714	0.92 (0.44-1.09)	0.816	2.40 (0.68-8.44)	0.172

TB - tuberculosis; HIV - Human Immunodeficiency Virus; AOR - Adjusted odds ratio

DISCUSSION

In this cross-sectional study on the distribution and determinants of different locations of EPTB, conducted in a country with high burden of both HIV infection and tuberculosis, we found a prevalence of isolated EPTB which was about 2/3rd of that for EPTB with pulmonary involvement. Overall, EPTB was found in 1/3rd of patients admitted for TB in the study unit. Compared with isolated pleural TB, HIV infection and longer duration of symptoms appeared to be the main indicators of lymph node and multifocal TB, with similar range of effects. Likewise, pulmonary involvement was positively associated with lymph node TB, and negatively associated with other focal EPTB.

Available published data suggest that EPTB accounts for 15% to 36% of all form of tuberculosis infection[2,3,9,14,15]. This proportion is much higher in settings with high prevalence of HIV infection, and can be as high as 50% in people with HIV infection[2,4,16]. The main clinical forms of EPTB found in our study were those frequently reported[2,4,10] Pleural and lymph node TB were the most frequent forms of EPTB in our population. Reported proportion of lymph node TB in other countries with high incidence of TB has ranged from 42% in Saudi Arabia [17], Turkish [18] and Nepal [19] to 17,6% in Taiwan [15]. In Ivory Coast, prevalence of pleural TB of 50% has been reported in patients followed by EPTB[9], while this proportion was just about 27% in a recent study from the US [14]. Pleural TB therefore, seems to be frequent in the context of high prevalence of TB-HIV co-infection. Unlike our study, genito-urinary and cutaneous TB are frequent clinical forms of EPTB in Hong-Kong, while in the US about 1/3rd of patients with EPTB have bone and joint TB[4,20].

HIV infection was present in about half of our population with EPTB. Variable prevalences of HIV-EPTB co-infection have been reported across settings. The prevalence of HIV infection in our patients with EPTB was twice higher than that of isolated pulmonary tuberculosis, in line with reports from a number of countries including Ivory Coast[9], USA[14] and South Korea[21]. However, other studies have reported no difference in the prevalence of HIV infection between patients with EPTB and those with isolated pulmonary tuberculosis[15,19]. Indeed, immune depression induced by HIV infection facilitates the dissemination of *Mycobacterium tuberculosis* out of the lungs and the reactivation of infection in extra-pulmonary organs[22].

HIV infection and longer duration of symptoms were independent predictors of lymph node and multifocal tuberculosis (as compared with pleural tuberculosis), in line with previous reports from the same centre[3], and elsewhere[10,23]. It has been suggested that acute chest pain, which is frequent during pleural tuberculosis may force patients with pleural tuberculosis to consult earlier than patients with other forms of EPTB[24]. We did not find an association between CD4 count and main locations of EPTB, likely reflecting that most of our patients with HIV infection were likely at an advanced stage of the disease, as evidenced by the low median CD4 count, similarly across EPTB sites. Unlike Leeds *et al*[10], we found a significant association between lymph node EPTB and concomitant pulmonary tuberculosis. Differential inclusion of patients with intra-thoracic lymph node tuberculosis in the sub-group of patients with lymph node TB may explain the discrepancy between the two studies.

LIMITATIONS

The present study has some limitations. Despite our efforts, we were unable to prove EPTB with certainty in about 9% of our participants. The presence among them of participants with no definitive diagnosis of EPTB may dilute some of the observed effects, which however would be only marginal given the likely small number of such patients in a specialised service. The study was restricted to only those patients hospitalised during the study period, who represented only about 1/3rd of all patients with tuberculosis followed at the centre during that period [25]. Our results may, therefore, not be generalizable to all patients with tuberculosis, particularly those receiving their treatment on an ambulatory basis. Our study, which, as far as we are aware, is the first of this kind on the determinants of main locations of EPTB in the settings of high prevalence of both HIV infection and tuberculosis,

was based on a reasonably good sample size and used robust analytic methods to investigate potential determinants of the disease.

CONCLUSIONS

In conclusion, about a third of patients hospitalised for tuberculosis in our setting have EPTB, with or without concomitant pulmonary involvement. Lymph node and pleural tuberculosis are the most frequent clinical forms of EPTB. Compared with pleural tuberculosis, patients with lymph node or disseminated tuberculosis are more likely to be HIV positive and to present late for diagnosis and treatment. In addition, patients with lymph node tuberculosis are more likely to have concomitant pulmonary involvement. Studies with a larger sample size are needed to investigate the impact of those factors and their control on the outcome of care for major EPTB locations in this setting.

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Case Report

NEUROTUBERCULOSIS MIMICKING BRAIN TUMOUR; A CASE REPORT

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(Received on 15.5.2012; Accepted after revision on 17.10.2012)

Summary: Neurotuberculosis is one of the grave complications of primary tuberculous infection. Extensive BCG vaccination of children and inadequate antituberculous drug therapy have led to the emergence of newer complex clinical pictures and diagnostic dilemma. Here we report a case of right-sided hemiparesis with features of raised intracranial tension in a six-year-old boy. Neuroimaging revealed presence of a high grade astrocytoma. On clinical examination, right-sided cervical lymphadenopathy with discharging sinus and tenderness over right hip joint were present. On further investigation, these were proved to be of tubercular origin. All preliminary findings were in favour of disseminated tuberculosis, but the nature of CNS lesion was creating diagnostic dilemma. Etiological diagnosis of the CNS lesion was necessary, as, if it was not of tubercular origin, the management protocol would be different and with any delay we could have lost the patient. Though on routine CSF study, no AFB were present, but we confirmed the presence of mycobacterial DNA by polymerase chain reaction. Patient showed considerable improvement after being put on Anti-tubercular Treatment (ATT) and steroids. Tuberculous brain abscess is rare. Very few cases have been reported even in adults. Most reported cases are in immunocompromised patients. This case highlights the fact that tuberculous brain abscess can have atypical presentation even in immunocompetent children mimicking CNS malignancy. Careful examination and thorough investigation are required to establish the diagnosis. Timely initiation of appropriate therapy can reduce mortality and neurological sequelae. **[*Indian J Tuberc 2013; 60:* 114 - 117]**

Key words: Neurotuberculosis, Astrocytoma

INTRODUCTION

Central nervous system (CNS) tuberculosis may present commonly as tuberculous meningitis or tuberculous mass lesions of which tuberculoma is more common and tuberculous brain abscess is rare[1]. In developing countries like India, burden of neurotuberculosis is very high but diagnostic facility limited. In this scenario, high degree of clinical suspicion to recognise uncommon presentations and implementation of practical and usable diagnostic tools is necessary for initiation of early treatment to prevent mortality and disabilities. Clinical response to ATT in all forms of neurotuberculosis is excellent if the diagnosis is made early before irreversible neurological deficit is established[2]. Here we report a case of a six-year-old child with right-sided hemiparesis initially suspected to have astrocytoma on neuroimaging, later on proved to be a case of tuberculous brain abscess.

CASE REPORT

A six-year-old male patient presented with fever for eight months and weakness of right side of body for three months. He had headache with repeated bouts, vomiting and focal convulsion for one week.

He had history of recurrent bilateral purulent ear discharge for the last three years and multiple neck swellings with intermittent discharge from one of those swellings.

His father had a history of pulmonary tuberculosis and completed ATT five years back.

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The child was incompletely immunised and no BCG scar was seen.

General examination revealed pallor, multiple, matted right cervical lymph nodes with discharging sinus.

On CNS examination, right-sided complete hemiparesis was present. Patient was conscious, obeying simple commands, no menigeal signs were present and no other cranial nerves were involved. However, right lower limb was found to be flexed, adducted and internally rotated and on further examination right anterior hip point was found to be tender.

Investigations revealed a normal chest X-Ray,CBC(Hb-9gm% ,TLC-8,400/cmm N- 40%, L-54%, E-6%), HIV ELISA was negative. C.S.F study (cell count- 285/cmm,70% mononuclear cells, 30% polymorphs, protein 357mg%, sugar 40 mg%, ADA-15 IU/L, Gram and AFB staining revealed no organism, PAP's stain showed no evidence of malignancy). FNAC of cervical lymph node showed cytomorphological features of caseation, degenerated epithelial cells suggestive of tuberculosis. Mantoux Test was positive (12*15mm). X-Ray right hip joint showed areas of rarefaction with increased joint space,capsular enhancement, with displaced fat planes suggestive of tuberculosis . CT brain showed large heterogenous, enhancing, ill-defined intracranial

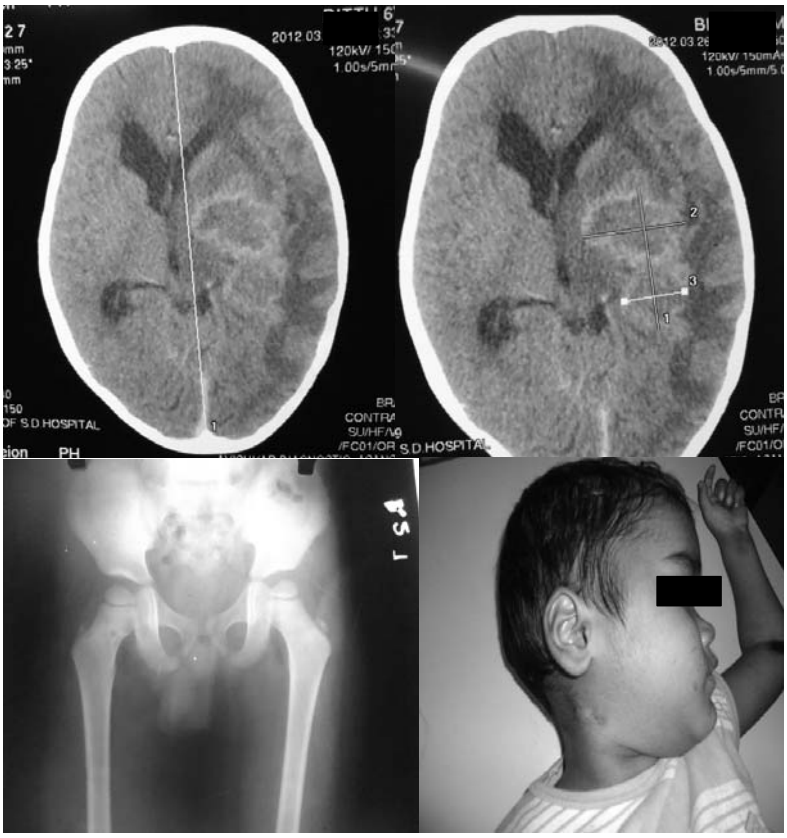

Figure 1: [A. B] CT brain showed large heterogenous, enhancing, ill defined intracranial SOL suggestive of astrocytoma with marked surrounding edema in left basal ganglia. There was extrinsic compression of 3rd ventricle with dilatation of lateral ventricles and mass effect leading to midline shift towards right.

[C]. X-Ray right hip joint showed areas of rarefaction with increased joint space,capsular enhancement, with displaced fat planes suggestive of tuberculosis .

[D]Multiple matted cervical lymphadenopathy with discharging sinus

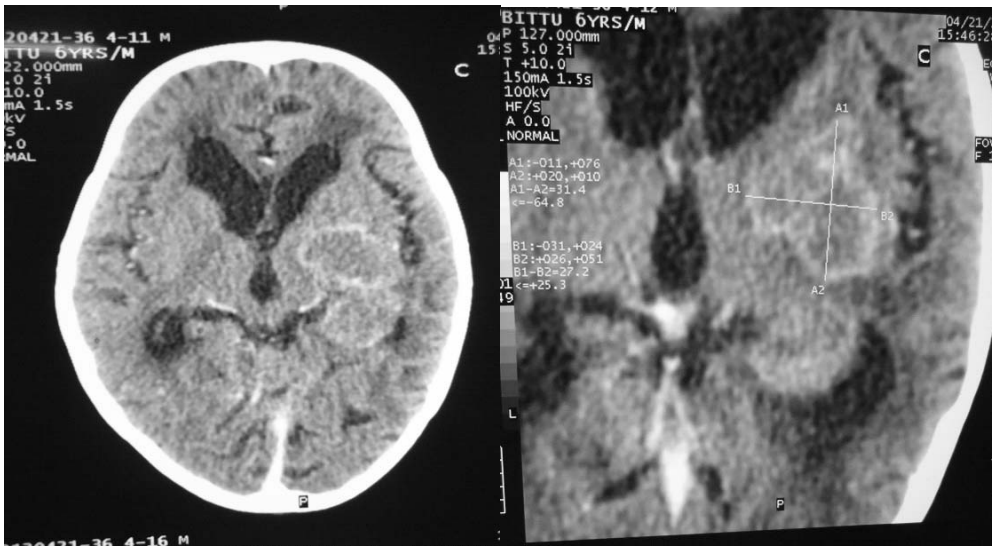

Figure 2: Repeat CT Brain after one month revealed a considerable improvement. There was a decrease in size of mass , no surrounding edema and minimal mass effect.

SOL with marked surrounding edema in left basal ganglia. There was extrinsic compression of third ventricle with dilatation of lateral ventricles and mass effect leading to midline shift towards right (Fig. 1). CT brain was suggestive of astrocytoma/ glioblastoma multiforme. MRI brain did not help any further. Since history and clinical features did not corroborate with radiological findings, PCR Study of CSF was done for detecting mycobacterial DNA which was positive.

There was no doubt about the presence of TB hip and lymph node TB, however the nature of intracranial SOL remained elusive. Also the decision to start chemotherapy and radiation was to be taken in case of brain tumour, any delay meant we would lose the patient. MRSpectroscopy would have been the investigation of choice but we could not avail it in our set up. History, clinical features and all other investigations except neuroimaging were in favour of neurotuberculosis and hence trial ATT with steroids was started. General well being , improved appetite was noted by parents and clinician within a fortnight. Repeat CT Brain (Fig. 2) after one month revealed a considerable improvement. There was a decrease in size of mass, no surrounding edema and minimal mass effect.

DISCUSSION

Neurotuberculosis is one of the serious manifestations of primary tuberculous infection. Though it accounts for only 1% of the total tuberculosis burden , it carries a high risk of mortality, morbidity and residual neurodeficit, especially in children. It is the most common type of chronic CNS infection in developing countries. Due to the varied presentations of neurotuberculosis, diagnosis is challenging, but diagnostic facility is limited. In this scenario, high degree of clinical suspicion is required to recognise uncommon presentations. Equally important is the implementation of practical and usable diagnostic tools for initiation of early treatment to prevent mortality and disabilities.

Tubercular meningitis is the most common presentation of CNS tuberculosis. Other common presentations are intracranial space occupying lesions such as tuberculoma and tubercular abscess, tubercular encephalopathy, tubercular vasculopathy. Our case was an atypical presentation of tubercular brain abscess.

The diagnosis of neurotuberculosis remains largely clinical and radiological, supported by an

appropriate cerebrospinal fluid (CSF) findings in patients with tuberculous meningitis. However, it gives variable results and sometimes even contraindicated in cases of tubercular space occupying lesion (SOL). Even in patients with large-volume CSF centrifugation from samples obtained by external ventricular drain, the yield of acid-fast bacilli is extremely low[3]. Guarded lumbar puncture was done in our case.

In neuroimaging, initial investigation is CECT brain. Superior to it are magnetic resonance imaging (MRI) and MR spectroscopy brain. Together they can be used to differentiate tuberculoma from other infective lesions such as brain abscess or neurocysticercosis and neoplastic lesions[4]. In MRI brain tuberculoma, tubercular abscess, astrocytoma can usually be differentiated. Tuberculoma shows high attenuation with ring enhancement. Tubercular abscess can be differentiated from tuberculoma by its central hyperintense T-2 weighed signal and more pronounced vasogenic edema. On the other hand, an astrocytoma usually has isointense solid components and hypointense cystic components with contrast enhancement. On MRI scans, this type of differentiation is possible because of the stage of the tuberculoma evolution namely, there is a non-caseating granuloma or caseating granuloma with a solid centre. On the other hand, when central liquefaction takes place, brain lesions may be indistinguishable from tuberculous brain abscess [5]. Furthermore, tuberculomas may show characteristics generally described in tuberculous brain abscess, including larger size (i.e., >3 cm in diameter), thin walls, presence of a single lesion, and multiloculation[6].

Other investigations, which may be helpful, are: gamma interferon assay , CSF culture, CSF Nucleic acid amplification tests (NAATs**)** for amplification of *Mycobacterium tuberculosis* specific DNA and detection of adenosine deaminase (ADA) in CSF (normal values 1-10 U/(L). NAATs detect mycobacteria nucleic acid in serum and CSF using the polymerase chain reaction (PCR) assay.[7] NAATs exhibit a high specificity (88%-100%), good positive predictive value and rapid processing. Due to its specificity, it could be used for treatment monitoring.

In our patient, tuberculosis of hip and lymphnode was diagnosed by basic investigations. Nature of the CNS lesion was contradictory, as it was more in favour of astrocytoma according to its appearance. Second closest diagnosis was tuberculous brain abscess, which was confirmed later on by demonstrating presence of mycobacterial DNA by PCR in CSF.

None of the current methods meet the criteria required by an efficient diagnostic test: rapid, accurate and readily applicable. Treatment in neurotuberculosis is therefore implemented according to the association of epidemiological, clinical criteria, bacteriological CSF examination and different complementary laboratory methods dependent on the technical level of each laboratory. The decision on which tests to use should consider country-level technical facilities and other relevant factors, such as cost and availability.

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Case Report

PYOPERICARDIUM DUE TO INFECTION WITH *MYCOBACTERIUM TUBERCULOSIS* - A RARE CASE REPORT

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(Received on 16.5.2012; Accepted after revision on 17.10.2012)

Summary: Pyopericardium or purulent pericarditis is a rare entity but usually associated with a high mortality. We report a case of 30-year-old male presenting with pyopericardium due to *Mycobacterium tuberculosis*. The patient was treated with Anti-tubercular therapy (ATT) alongwith pericardiocentesis and pericardiectomy. The patient responded well to treatment and recovered completely in due course of time. **[*Indian J Tuberc 2013; 60:* 118 - 120]**

INTRODUCTION

In the present antibiotic era, pyopericardium is uncommon. In many cases, it leads to constrictive pericarditis with a fatal outcome. A literature search found fewer than 40 cases of pyopericardium in adults.[1] Several aetiological agents like *Staphylococcus aureus, Streptococcus spp., Hemophilus influenzae, Pseudomonas spp.,coliforms* and anaerobic bacteria have been implicated. Tuberculosis is responsible for more than 50% of cases of pericarditis in developing countries where tuberculosis remains a major public health problem.[2] Historically, purulent pericarditis was seen most commonly as a complication of pneumonia in children and young adults.[3]

CASE REPORT

A 30-year-old male daily wage labourer by profession was admitted to our hospital with complaints of breathlessness, fever and mild retro sternal chest pain. On examination, the patient had raised JVP, muffled heart sounds, bilateral vesicular breath sounds, basal crepitations and rhonchi. The patient's vitals were stable. He had mild pallor, but was non-icteric.

The patient was non-diabetic, non-hypertensive but was addicted to alcohol for the past few years. No significant previous history of illness was reported including tuberculosis. Prior to this episode, the patient informed of respiratory tract infection one month back for which he received local treatment and the treatment details were not available.

Per abdominal examination revealed tender firm hepatomegaly, 2cm below the right coastal margin. Hemogram showed a TLC of 10,200 cells/cu.mm with neutrophils 80% and lymphocytes 20%. Hemoglobin was 10 gm/dl and Fasting blood sugar was 92 mg/dL. Serological tests including HIV and HBsAg were negative. Other tests including liver function tests were within normal limits.

Chest X ray showed enlarged cardiac silhouette with bottle shaped heart and right middle lobe consolidation (Figure-1). Echocardiography showed a large pericardial effusion with echogenic material without cardiac tamponade. The financial condition of the patient did not permit for a CT scan to be performed.

Pericardiocentesis was done and about 350 ml of fluid was aspirated. Pyopericardium was diagnosed at this stage based on the clinical findings, radiological investigations and the aspirated purulent pus. The pus was sent to Microbiology Department for examination. The pus was thick, purulent and

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creamy on gross appearance. Gram stain of the pus revealed plenty of lymphocytes with no micro-organisms seen. Ziehl Neelsen (ZN) and Auramine-rhodamine stain showed plenty of acid fast bacilli (Figure-2).

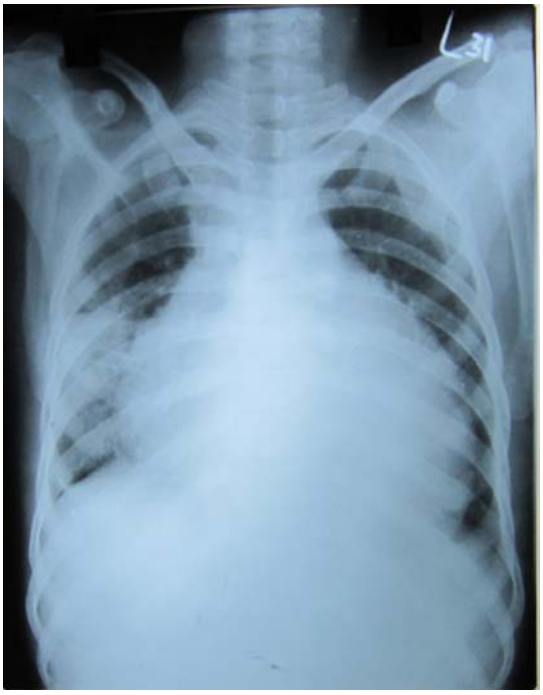

Figure 1: Chest X ray showing enlarged cardiac silhouette with bottle shaped heart and right middle lobe consolidation

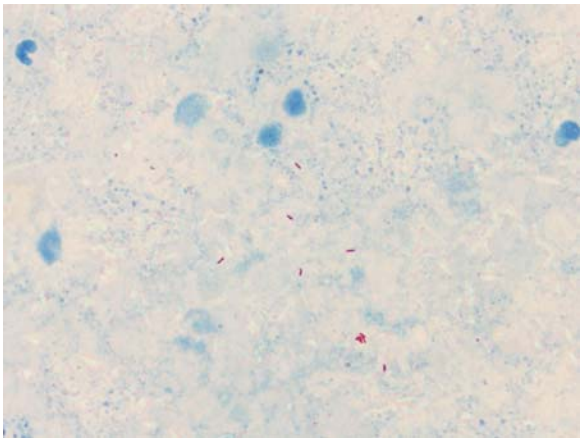

Figure 2: Z-N stain showing positive acid fast bacilli

Pus samples were inoculated into Sheep blood agar, Mac Conkey agar (for aerobic and anaerobic culture), LJ (Lowenstein Jensen) medium in duplicate one covered with black paper and SDA (Sabourauds dextrose agar) slants and incubated. There was no growth on the routine bacteriological media after 48 hours of both aerobic and anaerobic incubations.

A preliminary report based on gram stain, ZN stain, Auramine-rhodamine stain and absent growth on routine bacteriological culture was given basing upon which ATT was initiated in the patient. As per the National guidelines, the ATT regimen consisted of two month intensive therapy with four drugs (isoniazid, rifampicin, pyrazinamide, and ethambutol) followed by two drugs (isoniazid, rifampicin) in the maintenance phase for four months. The patient underwent a pericardiectomy and epicardiectomy without cardio pulmonary bypass and about 750 ml of pus was drained out.

The drained out pus was also processed in similar manner as the first aspirated pus and showed similar microbiological results. No fungal growth on SDA slants was observed even after four weeks of incubation.

The patient showed marked improvement and was discharged after 15 days of treatment with advice of continuation of ATT and regular follow up. The L-J medium was examined at frequent intervals and growth was observed on 25th day of incubation. This growth on L-J media was confirmed as *Mycobacterium tuberculosis* based on its growth pattern, duration of growth, staining and biochemical characteristics.

The clinician was intimated about *Mycobacterium tuberculosis* isolation and he informed that the patient was responding well to ATT treatment and had shown marked improvement with regard to the cardiological status on follow up.

DISCUSSION

Pericarditis is a common disorder that has multiple causes and presents in various clinical settings.[4] Purulent pericarditis or pyopericardium is diagnosed when pus is drained from the pericardial space or when bacteria are cultured from the pericardial fluid.[5]

Direct extension from pneumonia or empyema accounts for majority of cases but haematogenous spread during bacteremia, thoracic surgery and trauma can also cause pyopericardium.[6] In our case, the patient had an episode of respiratory tract infection one month prior to this episode which might have resulted in pyopericardium as evidenced by the right middle lobe consolidation features.

Pyopericardium cases have been reported worldwide due to different aetiologic agents.[1,7,9] A study by Krassas *et al* from Greece[1] and Farhat *et al* from France[9] have reported *Corynebacterium diphtheriae* and *Staphylococcus aureus* as the causative agents of pyopericardium from their cases respectively. *Mycobacterium tuberculosis* was identified in three of the cases of pyopericardium from a study conducted in Tanzania.[7]

The treatment is based on definitive surgical drainage (pericardiocentesis), pericardiectomy and epicardiectomy. The resection of pathological epicardium is usually performed to free the myocardium and prevent fibrosis. Usually, pericardiectomy without epicardiectomy should not be undertaken.[1] Medical treatment of pyopericardium involves mainly ATT and antibiotic therapy based on the causative organism isolated.

The low socio-economic status, professional exposure, nutritional status, alcoholism, previous episode of chest infection and increased prevalence of tuberculosis in this region may have contributed to the tuberculous pericarditis. To the best of our knowledge, this is the first case of Pyopericardium due to *Mycobacterium tuberculosis* reported from south Odisha.

There is a strong association between HIV infection and tuberculous pericarditis in endemic region where 40-75 % of patients with large pericardial effusion (suspected to be of tuberculosis) are infected with HIV.[2] A clinical study conducted in Africa also found cases of tuberculous pericarditis in HIV negative patients similar to our case which was HIV negative.[8]

In many cases, empirical treatment with ATT is initiated, especially in cases of large purulent peicarditis in developing countries like India without basing on the report of ZN stain. Despite the low isolation rates, *Mycobacterium tuberculosis* isolation from culture samples helps in diagnosis and treatment.

Purulent pericarditis or pyopericardium is an emergency condition which, when untreated, progresses to constrictive pericarditis or cardiac tamponade where the prognosis is usually fatal. This rare disease is often diagnosed late, when severe hemodynamic compromise develops due to pericardial tamponade.[9]

Timely judgement and diagnosis of the clinicians along with accurate microbiological diagnosis will definitely determine the prognosis. The case is reported for its rarity and possible clinical outcome.

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Case Report

EXTRAPULMONARY MULTIDRUG RESISTANT TUBERCULOSIS PRESENTING AS CHEST WALL ABSCESS –A RARE CASE REPORT

Mohan K Manu[1], Ashwini K. Mohapatra[2] and Rahul Magazine[1]

(Received on 25.7.2012; Accepted on 3.1.2013)

***Summary*:** Even though the prevalence of pulmonary drug resistant tuberculosis is showing an increasing trend globally, only a few case reports of extrapulmonary tuberculosis caused by drug resistant mycobacteria have been documented over the last decade. Extrapulmonary tuberculosis is not infrequent and may cause considerable morbidity and mortality. Tuberculous abscess over chest wall is commonly due to the spread from an adjacent affected lymph node group. Multidrug resistance poses a great challenge to the physicians in managing such a condition and significantly affects the prognosis. Here we report a rare presentation of multidrug resistant tuberculosis as anterior chest wall abscess in a young male. **[*Indian J Tuberc 2013; 60:* 121 - 123]**

Key words: Multidrug resistant Tuberculosis, Thoracic wall, Abscess.

INTRODUCTION

The term 'multidrug resistant tuberculosis' (MDRTB) is defined as *Mycobacterium tuberculosis* complex resistant to at least isoniazid and rifampicin.[1] Pulmonary form of MDRTB is widely reported but extrapulmonary forms of MDRTB are described sparsely in literature. Tuberculosis can affect any organ and lymph nodes are the commonest extrapulmonary manifestation reported.[2] Tuberculous chest wall abscess usually presents as an extension from the affected adjacent lymph node group or due to underlying bone involvement.

We report a case of a young male with multiple chest wall abscesses caused by multidrug resistant tuberculosis. This case assumes significance as the chest wall abscess is caused by multidrug resistant tubercle bacilli with no associated involvement of lung parenchyma and adjacent bony structures. This report also stresses the need for culture and drug sensitivity testing in every case of extrapulmonary tuberculosis along with histopathological investigation.

Clinical record

A 25-year-old male presented with swelling over left chest region of six months' duration. The swelling had gradually increased in size but was not associated with pain. He also complained of weight loss and intermittent fever, but cough and haemoptysis were not reported. He had no previous history of trauma. He was diagnosed with abdominal tuberculosis two years back and underwent standard anti-tubercular treatment (ATT) for nine months. Family history was non-contributory.

On examination, his vital signs were stable and pallor was present. There was no significant lymphadenopathy. A swelling of 15 x 10 cm was present over the left pectoral region with ill-defined borders (Figure 1), which was non-tender and soft in consistency. The skin over the swelling was normal. The swelling was fluctuant and non-transilluminant. There was no palpable bony defect underneath the swelling.

Complete blood count, urine routine and routine biochemistry were normal. He was

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found to be HIV negative. Chest radiograph (Figure 2) showed bilateral hilar adenopathy. Computed tomogram (CT) of thorax (Figure 3) revealed multiple large abscesses in the anterior chest wall overlying the manubrium and body of the sternum with intra-thoracic extension, left hilar lymphadenopathy, abdominal adenopathy and left psoas abscess, but no obvious pulmonary involvement. Fine needle aspiration from the swelling was done and yielded pus which on Ziehl Neelsen staining demonstrated Acid Fast Bacilli (AFB). Aerobic bacterial culture of the pus was sterile and cytology was negative for malignancy. AFB culture (Bactec) of the pus revealed *Mycobacterium tuberculosis* strain resistant to INH and Rifampicin. Pus was sent for mycobacteria molecular line probe assay test (LPA) (GenoType MTBDRplus, Hain Life Science, Nehren, Germany) which demonstrated *Mycobacterium tuberculosis* resistant to isoniazid (INH) and rifampicin. Thus the diagnosis of multidrug resistant tuberculosis (MDRTB) causing chest wall abscess was made. He was put on second line anti-tubercular drugs which comprised kanamycin, levofloxacin, ethionamide, para aminosalicylic acid (PAS) and ethambutol. He tolerated drugs well and after the intensive phase of six months, kanamycin and ethambutol were withdrawn. Patient has completed 18 months of continuation phase and is on regular follow up. He improved symptomatically, gained weight and the swelling reduced considerably in size (Figure 4).

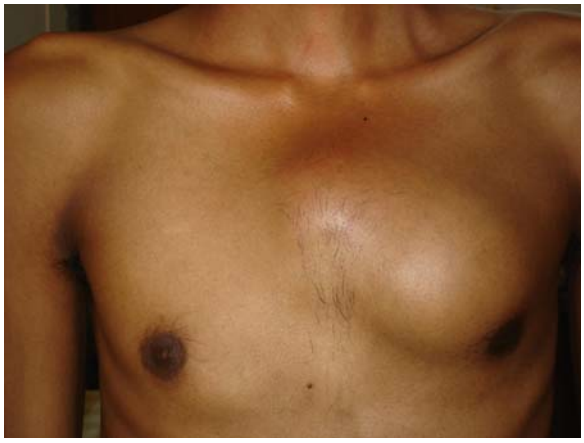

Figure 1: Photograph showing the anterior chest wall swelling.

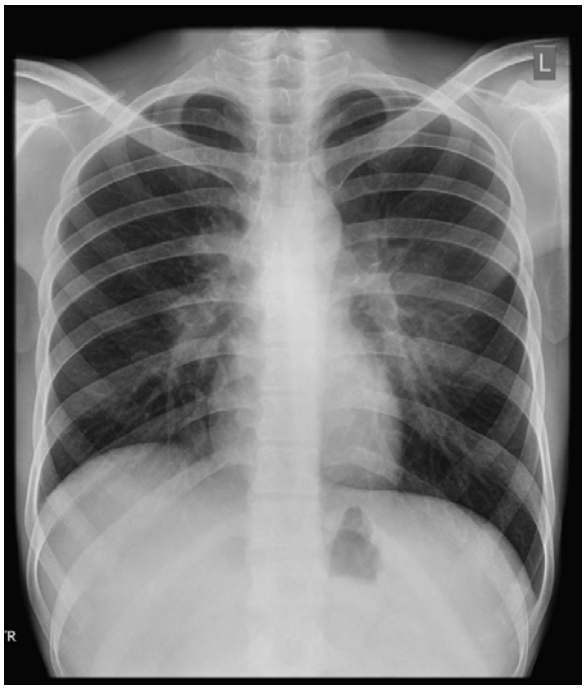

Figure 2: Chest X ray PA view showing normal lung fields and bilateral hilar adenopathy.

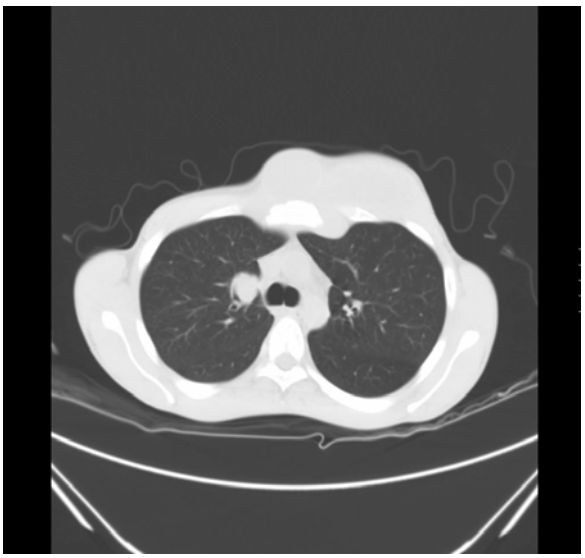

Figure 3: Computed tomogram (CT) of thorax showing multiple large abscesses in the anterior chest wall overlying the manubrium and body of the sternum with intra-thoracic extension, left hilar lymphadenopathy.

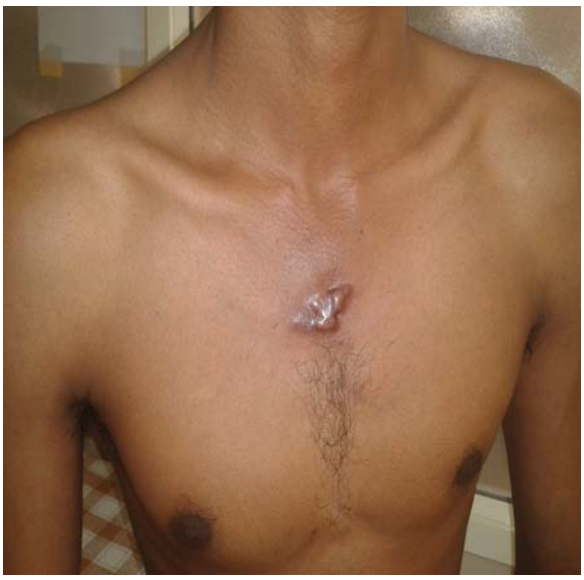

Figure 4: Photograph taken after completion of treatment showing reduction in size of the chest wall swelling.

DISCUSSION

Extrapulmonary Tuberculosis accounts for roughly 15% of Tuberculosis (TB) cases among immunocompetent hosts and for 50-70% of cases of TB occurring in immunocompromised, especially in persons with HIV. TB can affect any organ system and high index of suspicion is required for proper diagnosis, especially in extrapulmonary disease. MDRTB is a strain of *Mycobacterium tuberculosis* resistant to first line anti-tubercular drugs, at least isoniazid and rifampicin. Pulmonary tuberculosis due to MDRTB is a serious public health concern and is one of the reasons that hamper tuberculosis eradication. According to World Health Organization (WHO) in 2010, there were around 650,000 cases of MDR-TB among the world's 12 million prevalent cases of TB. In India, MDRTB accounts for 2.1% and 15% of the newly detected smear positive tuberculosis and retreatment TB cases respectively.[1] In immunocompromised host, extrapulmonary form of tuberculosis is more common.[2] Tuberculosis affecting lymph nodes is the commonest form of extrapulmonary tuberculosis. The common aetiological infectious agents of chest wall abscesses are *Mycobacterium tuberculosis*, Actinomyces sp., fungi, and other aerobic and anaerobic bacteria.[3] Tuberculous chest wall abscess develops usually due to spread from adjacent lymph node group. Internal mammary nodes are found to be the most commonly involved. Tuberculous abscesses of the chest wall can involve the sternum, costochondral junctions, rib shafts, costovertebral joints and the vertebrae. They are most frequently found at the margins of the sternum and along the rib shafts.[4] Extrapulmonary tuberculosis cases due to MDRTB are reported, but rare.[2, 5-7] In our case, the patient had chest wall abscess due to MDRTB. He had undergone anti-tubercular treatment for abdominal tuberculosis two years ago. Extrapulmonary tuberculosis usually responds to chemotherapy satisfactorily whereas extrapulmonary MDRTB cases require longer duration of treatment with toxic and expensive drugs. The response to second line drug therapy in extrapulmonary MDRTB was satisfactory in our case. **This case stresses on the need for proper investigations, not only routine bacterial culture of pus, but mycobacterial culture and sensitivity of aspirate, especially when patient had past history of anti-tubercular chemotherapy, keeping in mind the chance of MDRTB.**

ACKNOWLEDGEMENTS

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Short Communication

DETECTION OF MYCOBACTERIAL DNA DIRECTLY FROM FNAC SAMPLES OF TUBERCULOUS LYMPHADENOPATHY USING REAL-TIME PCR: A PRELIMINARY STUDY

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(Received on 14.8.2011; Accepted after revision on 10.1.2013)

Summary

Background: Fine needle aspiration cytology (FNAC) is most commonly used in first line investigation for tuberculous lymphadenopathy (TBLAP). Real-time polymerase chain reaction (PCR) an extremely versatile technique is being used for diagnosis and follow up of patients with infectious diseases. It can also be used for detecting *Mycobacterium tuberculosis* (*Mtb*) DNA in FNAC samples of TBLAP for rapid diagnosis and treatment.

Aim: Detection of *Mtb* DNA on FNAC samples of tuberculous lymphadenopathy using Real-time PCR.

Material and Methods: Twelve clinico-cytologically diagnosed TBLAP cases and five controls were included in the study. FNA samples were used for studying morphology, AFB demonstration, culture and for detecting *Mtb* DNA using Real-time PCR.

Results*: Mtb* DNA was detected in ten cases (83.33 %) by Real-time PCR. ZN stain was positive in eight cases and culture in six cases.

Conclusion: Detection of *Mtb* DNA in FNAC samples using Real-time PCR is a time saving, logical, economical approach over the culture based method. **[*Indian J Tuberc 2013; 60:* 124 - 127]**

Key words: FNAC, Tuberculosis lymphadenopathy, Real-time PCR

INTRODUCTION

Rapid and accurate diagnosis of Tuberculosis is of utmost importance for control of Tuberculosis. Conventional tuberculous lymphadenopathy (TBLAP) diagnostic methods (smear positivity, culture/histopathology) have known limitations and are time-consuming. Real-time PCR, a versatile technique is being increasingly used for detection of micro-organisms including *M. tuberculosis*.[1] Fine needle aspiration cytology (FNAC), a widely practised non-invasive, safe, simple and rapid first line investigative method for LAP can be combined with fast and reliable technique like real-time PCR for early diagnosis and efficient management of TBLAP. In the present study real-time PCR was used to detect *Mtb* DNA in FNAC samples of TBLAP.

MATERIAL AND METHODS

This preliminary study was conducted in Guru Teg Bahadur Hospital, New Delhi over three months. Twelve clinico-cytologically confirmed patients, not started on ATT were included as cases. The cytologic diagnosis of TBLAP was made on the presence of epithelioid granulomas with necrosis (criteria followed in previous studies[2,3]) and/or AFB positivity. The five controls included two diagnosed cases of lymphoma, metastatic carcinoma with necrosis each and one case of pyogenic abscess (gram stain positive for cocci). The FNA material was used for i) studying cytomorphology (May Grunwald Geimsa Smears), ii) AFB screening (ZN smears), iii) Gram Staining (exclusion of other micro organisms), iv) culture on L-J slant and v) Real-time PCR (detection of *Mtb* DNA).

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DNA EXTRACTION

Mycobacterial genomic DNA was extracted as previously described.[4] DNA extracted from 12 cases of TBLAP and five controls was run on Real- time PCR to detect *Mtb* DNA. Real-time PCR methods are based on hybridization of nucleic acids with fluorescent-labeled probes spanning DNA regions of interest.[5] Monitoring the fluorescent signals which increase in intensity directly proportionate to the amount of amplified product during the PCR run allows the detection and quantitation of the accumulating product in real time. Rotor Gene 3000 and 6000 series was used for the Real-time PCR. M*tb* DNA was amplified using the Genosen's *Mtbs* Complex Real-time PCR Kit.

RESULTS

Clinical Features

The age of the patients in the study ranged from 11 to 50 years with peak incidence in the second and third decades. Cervical LAP (50%), single lymph node enlargement (70%) and LAP with fever (68.5%) were the most common clinical presentations. Aspirate was thick cheesy in eight cases, thin purulent and hemorrhagic in two cases each. Maximum cases (80%) yielded 0.2-0.5ml FNA material. Eighty per cent FNAC smears showed epithelioid granuloma with caseous necrosis on cytology. 67% cases were AFB positive. None of the controls were AFB positive. *Mtb* could be isolated in 50% cases by culture.

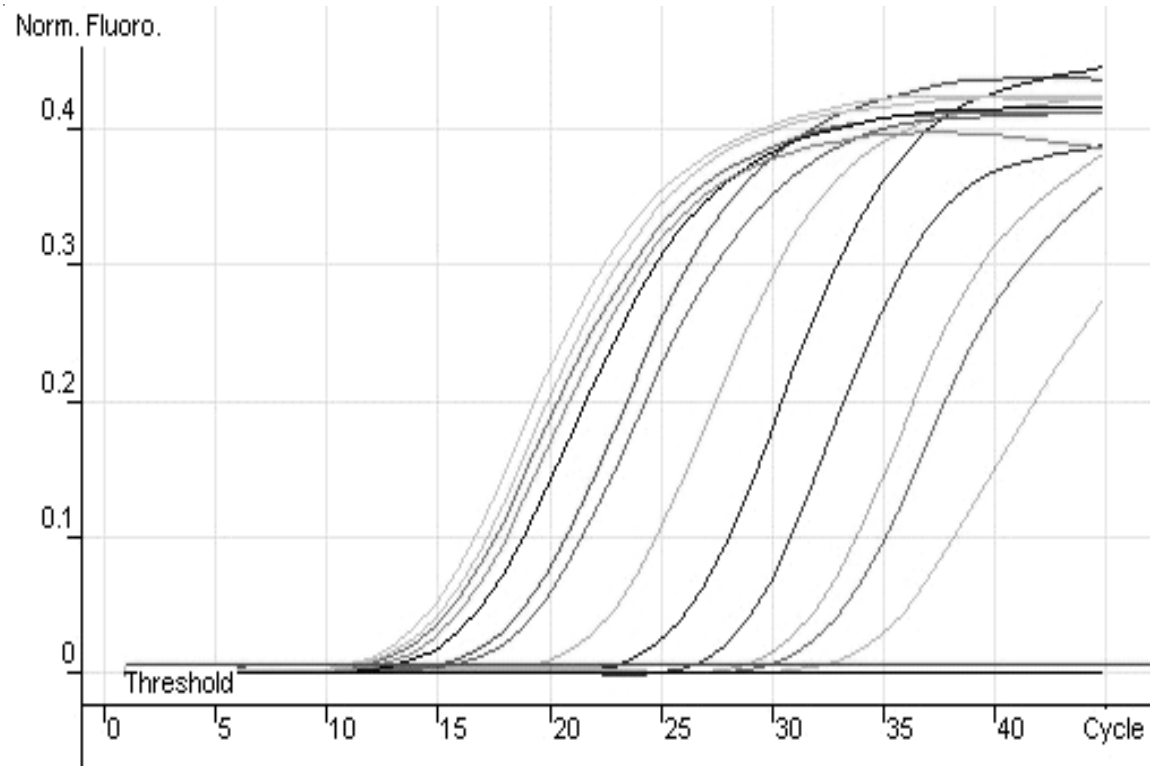

Figure: Real-time PCR Results for MTB DNA
Amplification curves for *M.tuberculosis* DNA (Cycle Threshold)
"S' shaped curve indicating exponential amplification in *Mtb* DNA positive samples

Table: Real-time PCR results showing cycle threshold and copies of DNA generated

No.	Colour	Name	Type	Ct	Given Conc (copies/ul)	Calc Conc (copies/ul)	% Var
1		s1 MTUBERCULOSIS	Standard	15.52	100000	113861	13.9%
2		S2	Standard	19.69	10000	8718	12.8%
3		S3	Standard	23.40	1000	891	10.9%
4		S4	Standard	26.75	100	113	13.0%
5		Sample 1	Unknown	32.72		3	
6		Sample 2	Unknown	30.25		13	
7		Sample 3	Unknown	28.35		15	
8		Sample 4	Unknown	29.12		26	
9		Sample 5	Unknown	16.27		71782	
10		Sample 6	Unknown	12.17		896609	
11		Sample 7	Unknown	13.57		378840	
12		Sample 8	Unknown	12.75		626280	
13		Sample 9	Unknown	11.41		1426917	
14		Sample 10	Unknown	11.84		1095210	
15		Sample 11	Unknown	11.89		1087560	
16		Sample 12	Unknown	12.67		632179	
17		NC	NTC				

This report generated by Rotor-Gene Real-Time Analysis Software 6.0 (Build 41)

Real- time PCR could pick up *Mtb* DNA in 10 out of 12 cases. The results are shown below in the Figure which depicts the exponential amplification of cDNA in M*tb* positive cases and the linear relationship between the DNA amplification and cycle number. Table above represents the analyzed data showing the cycle number and exact copies of cDNA generated. Samples with less M*tb* DNA show higher cycle number.

DISCUSSION

Early detection and effective treatment are the two key factors mandatory for better control of tuberculosis. ZN staining for AFB of clinical material, the most frequently used conventional method, exhibits low sensitivity (10-20%).[6] Culture is specific but is time-consuming (four-eight weeks) , not very sensitive (<50%),[6] and requires viable organism which is often a problem with partially treated patients and pauci-bacillary cases.[7] To overcome these shortcomings of conventional methods, real-time PCR is a promising approach for rapid detection of *Mtb* DNA in clinical samples. In Real-time PCR, fluorescent-labelled probes amplify DNA and the reaction is quantified in real time lowering risk of carry over and cross contamination.[5] The reported sensitivity of real-time PCR in clinical specimens has ranged from 71.6 to 98.1 per cent[8] with specificity close to 100%.[9] Being a highly sensitive assay which

does not need viable bacteria, it can be very useful in timely diagnosis of paucibacillary and partially treated cases.[10] The advantage of Real-time PCR over conventional agarose-gel PCR is that it is rapid and quantitative.[5] The main handicap of the assay is the need for well-equipped laboratory facility and trained personnel.

The study used Real-time PCR to detect *Mtb* DNA directly from FNAC samples from TBLAP patients**.** The assay detected *Mtb* DNA in 10 out of 12 samples (83.33%). The PCR detected *Mtb* DNA in AFB negative cases, proving the greater sensitivity of Real-time PCR over ZN staining. Real-time PCR picked up *Mtb* DNA in four culture negative cases indicating that viable organisms are not pre-requisites for the assay. It is useful in detecting partly treated patients that may not harbour live bacilli. The assay did not miss any of the smear/culture-positive cases. Thus, Real-time PCR is a very sensitive and specific method. We could detect as low as three copies of *Mtb* DNA in the samples making this technique helpful in paucibacillary cases. Exact number of copies present in each sample could be analysed ranging from merely three to over ten million copies. Hence Real-time PCR is not only sensitive and specific but also a quantitative method.

Negative PCR results seen in two samples may be either due to inhibitors of *Taq* polymerase or sampling difficulties. It is known that the initial DNA volume and the irregular distribution of bacilli in the clinical specimens affect the sensitivity of the test.[11] Small sample yield (<0.5ml in 80% samples) may have affected the results to some extent. Studies[12] mention that presence of inhibitors in the clinical samples (like TBLAP) interferes with amplification-based techniques affecting the DNA extraction, leading to false negative results.

Conventional methods of diagnosing tuberculosis are time-consuming, less specific and sensitive. **The combined use of FNAC, a simple, safe and non-invasive method with Real-time PCR, a rapid, sensitive, specific and state of the art technique can give an additional advantage for timely diagnosis and effective management of tuberculosis.**

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Indian J Tuberc 2013; 60: 128 - 129

SIXTY SEVENTH NATIONAL CONFERENCE ON TUBERCULOSIS AND CHEST DISEASES (NATCON – 2012): A BRIEF REVIEW

J.N. Banavaliker*

The 67th National Conference on Tuberculosis and Chest Diseases (NATCON 2012) was organized by the Bihar Tuberculosis Association (BTA) under the auspices of the Tuberculosis Association of India (TAI) from 8th to 10th February, 2013. The venue of the Conference was Mahavir Cancer Sansthan, Patna. Shri. U.N. Vidyarthi, Organizing Chairman and Dr. Rajiva Ranjan, Organizing Secretary and their team worked hard to make the conference a grand success. The team worked under the overall advice and guidance of Dr. J.N. Banavaliker, Vice Chairman of Tuberculosis Association of India. Over 300 delegates attended the Conference.

The conference was inaugurated by Sri Ashwini Kumar Choubey, Hon'ble Minister, Health & Family Welfare, Government of Bihar. Sri Vijay Kumar Chaudhary, Hon'ble Minister, Water Resources, Government of Bihar graced the occasion. A souvenir was also brought out on the occasion.

Delivering his presidential address, Dr. Rajendra Prasad deliberated on some of the facts and issues that are of great national importance in today's context, viz. burden of tuberculosis, TB Control, Future Plan, Drug Resistant Tuberculosis, TB & HIV, Challenges in TB Control, TB & Diabetes, Smoking and TB and other lung diseases, Air Pollution & TB, Indoor air pollution, burden of non-tubercular respiratory diseases, lung cancer, Respiratory Intensive Care, Medical Education, etc.

Key note address was delivered by Dr. Jagdish Prasad, Director General of Health Services and Chairman, Tuberculosis Association of India. Dr. Prasad highlighted the problem of tuberculosis in Bihar state and the project about involvement of retail pharmacists in RNTCP implementation. 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, drew attention of the gathering towards TB-HIV co-infection and the alarming effects of drug resistant tuberculosis globally. TB is a major cause of death in HIV infected persons and HIV infection on the other hand is the most potent risk factor for developing active Tuberculosis. Though TB is a curable and preventable disease and highly effective treatment regimens are available, yet it continues to be the most dreaded public health problem world over, said Dr. Agarwal.

Dr. Rajiva Ranjan, Organizing Secretary of the Conference, read out the citations for various awards of TAI which were presented to the recipients by the Hon'ble Ministers. The inaugural function ended with a vote of thanks by Shri U.N. Vidyarthi, Chairman, Bihar TB Association.

The Scientific Programme of the Conference was very lively, informative and educative covering almost all the important aspects of tuberculous and non-tuberculous chest diseases. Besides three prestigious orations, about 15 guest lectures and two panel discussions, there were about 80 oral paper presentations, including award papers and about 15 poster presentations. Dr. P.K. Sen TAI Gold Medal Oration was delivered by Dr.Rohit Sarin, Director, LRS Institute of TB and Respiratory Diseases on the subject of "MDR TB - Challenges in Management". Lupin-TAI Oration was delivered by Dr. S.K. Jindal, Senior Professor & Head, Department of Pulmonary Medicine, PGI, Chandigarh on the subject of "Advances in Management of Tuberculosis-2013". Dr. S.N. Tripathy Memorial

* Vice-Chairman, Tuberculosis Association of India

Oration was delivered by Dr. Bamin Tada on the subject of "Critical issues and challenges in TB Control Programme in India". The panel discussion on "Management of COPD - Newer Modalities" moderated by Dr. V.K. Arora, Honorary Technical Adviser, TAI, was thought-provoking and attracted a huge applause and generated a lot of enthusiasm among the delegates.

Drug resistance in TB was highlighted by two important Guest lectures - one on "MDR-TB" by Prof. Rajendra Prasad, President of the Conference and on "XDR-TB" by Dr. J.N. Banavaliker, Vice-Chairman, TB Association of India. They emphasized the importance of early detection and effective management of cases to prevent further transmission.

RNTCP session was coordinated by Dr. Rohit Sarin, Director, LRS Institute of Tuberculosis and Respiratory Diseases. He introduced the latest developments of programme and also explained his future vision about the programme. Two speakers during the session deliberated on ''Trained Manpower Development challenges under RNTCP' and 'Monitoring and Supervision Challenges'. The session generated lot of fruitful discussion among speakers and delegates. Dr. Sarin 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, viz. "Changing landscape of TB Control and role of NGOs" and "Innovatively involving NGOs in TB Control – Experience from India".

The meetings of the Standing Technical Committee (STC) and Secretaries of State TB Associations were held on 9th February, 2013. The STC meeting selected subjects for NATCON 2013 and discussed about its venue in addition to other discussions. The discussions in the Secretaries' meeting mainly revolved around TB Seal Campaign.

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 2012 held in Patna 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 Bihar were the highlights of the various meals wherein different menu was served on different days.

In the Business and Concluding Session, Dr. Rajendra Prasad, President of the Conference, 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 participated in large numbers and evinced keen interest in presenting papers of good quality. Another noteworthy feature of the conference was more involvement of local speakers from private sector.

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

Drs. Bamin Tada and K.K. Chopra proposed a vote of thanks on behalf of the delegates and Shri Vidyarthi on behalf of the Organising Committee.

Indian J Tuberc 2013; 60: 130 - 133

ABSTRACTS

Treatment Practices in Pulmonary Tuberculosis by Private Sector Physicians of Meerut, Uttar Pradesh

A. Yadav, S.K. Garg, H. Chopra, S.K. Bajpai, T. Bano, S. Jain and A. Kumar. *Indian J Chest Dis Allied Sci* 2012; **54**: 161-3.

Majority of the qualified medical practitioners in the country are in the private sector and more than half of patients with tuberculosis (TB) seek treatment from them. The present study was conducted with the objective of assessing the treatment modalities in pulmonary tuberculosis by the private physicians in Meerut City, Uttar Pradesh, India. A cross-sectional study was carried out covering all the private physicians (graduates and postgraduates in Medicine and Chest Diseases) registered under the Indian Medical Association, Meerut Branch (n=154). The physicians were interviewed by a pre-designed and pre-tested questionnaire about the treatment modalities practised by them. Only 43.5% private physicians had attended any Revised National Tuberculosis Control Programme (RNTCP) training in the past five years. Only 33.1% of them were aware of the International Standards of Tuberculosis Care (ISTC). Fifty-three different regimens were used to treat the patients. Majority of physicians (76%) prescribed daily regimens while 24% administered both daily and intermittent treatments. None of the private physicians prescribed exclusive intermittent regimen. Eighty-seven different treatment regimens were used for the treatment of multidrug-resistant TB (MDR- TB) with none of them prescribing standard treatment under RNTCP. As majority of private practitioners do not follow RNTCP guidelines for treating TB, there is an urgent need for their continued education in this area.

Spatial Clusters of Nontuberculous Mycobacterial Lung Disease in the United States

Jennifer Adjemian, Kenneth N. Olivier, Amy E. Seitz, Joseph O. Falkinham, Steven M. Holland and D. Rebecca Prevots. *Am J Respir Crit Care Med* 2012; **186**: 553-8.

Prevalence of pulmonary non-tuberculous mycobacterial (PNTM) disease varies by geographic region, yet the factors driving these differences remain largely unknown. The objectives were to identify spatial clusters of PNTM disease at the county level and to describe environmental and sociodemographic factors predictive of disease. PNTM cases identified from a nationally representative sample of Medicare Part B beneficiaries from 1997 to 2007 were geocoded by county and state of residence. County-level PNTM case counts and Medicare population data were then uploaded into SaTScan to identify significant spatial clusters and low-risk areas of disease. High-risk and low-risk counties were then compared to identify significant sociodemographic and environmental differences. We identified seven significant ($P < 0.05$) clusters of PNTM cases. These high-risk areas encompassed 55 counties in eight states, including parts of California, Florida, Hawaii, Louisiana, New York, Oklahoma, Pennsylvania, and Wisconsin. Five low-risk areas were also identified, which encompassed 746 counties in 23 states, mostly in the Midwest. Counties in high-risk areas were significantly larger, had greater population densities, and higher education and income levels than low-risk counties. High-risk counties also had higher mean daily potential evapotranspiration levels and percentages covered by surface water, and were more likely to have greater copper and sodium levels in the soil, although lower manganese levels. Specific environmental factors related to soil and water exposure

appear to increase the risk of PNTM infection. Still, given that environmental sources of NTM are ubiquitous and PNTM disease is rare, both host susceptibility and environmental factors must be considered in explaining disease development.

A multicentric study on chronic cough in children: Burden and aetiologies based on a standardized management pathway

Anne B. Chang, Colin F. Robertson, Peter P. Van Asperen, Nicholas J. Glasgow, Craig M. Mellis, I. Brent Masters, Laurel Teoh, Irene Tjhung, Peter S. Morris, Helen L. Petsky, Carol Willis and Lou I. Landau. *Chest* 2012; **142(4)**: 943-50.

While the burden of chronic cough in children has been documented, aetiologic factors across multiple settings and age have not been described. In children with chronic cough, we aimed (1) to evaluate the burden and aetiologies using a standard management pathway in various settings, and (2) to determine the influence of age and setting on disease burden and etiologies and etiology on disease burden. We hypothesized that the etiology, but not the burden, of chronic cough in children is dependent on the clinical setting and age. From five major hospitals and three rural-remote clinics, 346 children (mean age 4.5 years) newly referred with chronic cough (> 4 weeks) were prospectively managed in accordance with an evidence-based cough algorithm. We used a priori definitions, timeframes, and validated outcome measures (parent-proxy cough-specific quality of life [PC-QOL], a generic QOL [pediatric quality of life (PedsQL)], and cough diary). The burden of chronic cough (PC-QOL, cough duration) significantly differed between settings (P = .014, 0.021, respectively), but was not influenced by age or etiology. PC-QOL and PedsQL did not correlate with age. The frequency of etiologies was significantly different in dissimilar settings (P = .0001); 17.6% of children had a serious underlying diagnosis (bronchiectasis, aspiration, cystic fibrosis). Except for protracted bacterial bronchitis, the frequency of other common diagnoses (asthma, bronchiectasis, resolved without specific-diagnosis) was similar across age categories. The high burden of cough is independent of children's age and aetiology but dependent on clinical setting. Irrespective of setting and age, children with chronic cough should be carefully evaluated and child-specific evidence-based algorithms used.

Pharmacokinetic/pharmacodynamic parameters and the choice of high-dosage rifamycins

D.A. Mitchison. *The International Journal of Tuberculosis and Lung Disease* 2012; **16(9)**: 1186-9.

Clinical trials and the behaviour of bacterial persisters were the settings. The objective was to explain why the efficacies of isoniazid (INH) and rifamycins during the treatment of tuberculosis (TB) are related not to the area under the curve (AUC)/ minimum inhibitory concentration (MIC), but to peak drug concentrations. We examined the response in clinical trials with patients treated with INH alone and divided into slow and rapid acetylators of INH. The efficacy of INH is best related to peak concentrations, as repeated peaks can kill low-degree resistant mutants. A similar process might result in repeated peak concentrations of rifamycins killing low-tolerance persisters. If the efficacy of rifamycins is best related to peak concentrations, we can explain the discrepancy between mouse studies on daily rifapentine (RPT) and the failure to accelerate elimination of TB from sputum in the TBTC Study 29A, as daily RPT greatly increases the AUC but not the peak concentrations. High dosage rifampicin may be better able than RPT to cause high peaks.

Long-term follow-up of contacts exposed to multidrug-resistant tuberculosis in Victoria, Australia, 1995-2010

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The effectiveness of public health strategies following exposure to multidrug-resistant tuberculosis (MDR-TB) is not clear. The objective

was to perform long-term follow-up of MDR-TB contacts and review individual outcomes and management approaches. It was a retrospective review of MDR-TB contacts identified by the Victorian Department of Health from 1995 to 2010. Health records, including personal medical and pharmacy records and statewide clinical and laboratory TB databases, were searched to identify management strategies and individual outcomes. A total of 570 contacts of 47 MDR-TB cases were identified, with a total follow-up period of 3093 person-years of observation (PYO) since exposure. Of 570 contacts, 49 (8.6%) were considered likely to have been infected with *Mycobacterium tuberculosis* from index cases, and 11/49 (22.5%) of these were prescribed preventive therapy tailored to isolate susceptibility. No MDR-TB cases occurred in those receiving preventive treatment, while two cases were observed in those not treated (incidence 2878/100000 PYO during the first 2 years post exposure). The risk of MDR-TB transmission to close contacts in this low-prevalence setting highlights the potential for public health strategies involving preventive treatment.

Risk and outcome of multidrug-resistant tuberculosis: vitamin D receptor polymorphisms and serum 25(OH)D

J. Rathored, S. Sharma, B. Singh, J.N. Banavaliker, V. Sreenivas, A.K. Srivastava, A. Mohan, A. Sachan, C.V. Harinarayan and Goswami. *The International Journal of Tuberculosis and Lung Disease* 2012; **16(11)**: 1522-8.

All India Institute of Medical Sciences and Rajan Babu Institute of Pulmonary Medicine and Tuberculosis, New Delhi, India were the settings. The objective was to investigate the association of vitamin D receptor (VDR) polymorphisms and serum 25(OH)D with susceptibility to, and response to treatment of, multidrug-resistant tuberculosis (MDR-TB) in comparison with drug-susceptible pulmonary TB (DS-PTB) and healthy controls. It was a cross-sectional study. A total of 897 participants from northern India were consecutively enrolled into three groups (MDR-TB 354, DS-PTB 338, controls 205). Genotypic and allelic frequencies of FokI, BsmI and TaqI VDR polymorphisms, and serum 25(OH)D, calcium and intact parathyroid hormone were measured in all participants. In those with active TB, disease severity, time to sputum smear and culture conversion were correlated with VDR genotype and biochemical parameters. FokI Ff genotype and TaqI t allele correlated positively with MDR-TB; ff genotype and f allele of FokI frequency were higher in both TB groups. BsmI Bb genotype correlated inversely with MDR-TB. Serum 25(OH)D concentrations were significantly the lowest in MDR-TB, correlating inversely with time to sputum smear conversion. VDR gene polymorphisms and hypovitaminosis D may predispose to MDR-TB. Lower serum 25(OH)D may increase time to MDR-TB sputum smear negativity.

Screening tuberculosis patients for diabetes mellitus in Fiji: notes from the field

S. Gounder and A.D. Harries. *Public Health Action* 2012; **2(4)**: 145-7.

Diabetes (DM) is a problem in Fiji and threatens tuberculosis (TB) control efforts. A review was conducted of all TB patients registered in Fiji in 2011 to assess routine practices of screening for DM. Of 221 TB patients, 138 (62%) had their DM status recorded in their case folders; 18 (13%) had a known history of DM. Random blood glucose (RBG) was performed in 91 (76%) of the remaining 120 patients: 47(52%) had RBG $\geq$ 6.1 mmol/l, but only three were further investigated, of whom one was diagnosed with DM. There are deficiencies in screening TB patients for DM in Fiji, and improvements are needed.

Lessons from a randomised clinical trial for multidrug-resistant tuberculosis

N. Padayatchi, W.R. Mac Kenzie, Y. Hirsch-Moverman, P.J. Feng, E. Villarino,J. Saukkonen, C.M. Heilig, M. Weiner and W.M. El-Sadr. *The International Journal of Tuberculosis and Lung Disease* 2012; **16(12)**: 1582-7.

The treatment of multidrug-resistant tuberculosis (MDR-TB) is currently based upon

expert opinion and findings from case series, rather than upon randomised clinical trials (RCTs). The objective was to describe the challenges encountered during an RCT for the treatment of MDR-TB. Tuberculosis Trials Consortium Study 30 was a pilot, Phase I/II, double-blind, placebo-controlled, RCT of the safety and tolerability of 16 weeks of daily, low-dose linezolid treatment for MDR-TB. A total of 36 patients, 56% of the target of 64 patients, consented to participate, for an average of 0.69 enrolments per week. Of the 36 patients enrolled, only 25 (69%) completed at least 90 doses of study treatment. Among the 12 (33%) patients who did not complete all 112 doses of the study treatment, the median time to study withdrawal was 15 days (range 0-92). After the study, we discovered discordance between treatment assignment and study drug for at least nine (25%) of the 36 patients. Recruitment and retention in this MDR-TB clinical trial posed substantial challenges, suggesting the need for a large, multidisciplinary group of study staff to support the participants. Withdrawal tended to occur early in study treatment. The discrepancy in assigned study medication reflects the need for stronger administrative controls for study drugs.

Extensively drug-resistant tuberculosis in India: A review

Joy Sarojini Michael and T. Jacob John. *Indian J Med Res* 2012; **136(4)**: 599-604.

Extensively drug resistant tuberculosis (XDR- TB) has become a new threat for the control of TB in many countries including India. Its prevalence is not known in India as there is no nation-wide surveillance. However, there have been some reports from various hospitals in the country. We have reviewed the studies/information available in the public domain and found data from 10 tertiary care centres in nine cities in India. A total of 598 isolates of XDR *Mycobacterium tuberculosis* have been reported in the studies included. However, the reliability of microbiological methods used in these studies was not checked and thus the XDR- TB data remained invalidated in reference laboratories. Systematic surveillance and containment interventions are urgently needed.

XDR- TB in India

The above write up on extensively drug resistant tuberculosis in India -a review by Drs Joy Sarojini Michael and T. Jacob John is an interesting attempt to focus on a problem which generates very diverse actions among people, scientific leaders, clinicians and public health personnel. As these reports are based on various tertiary care hospitals, these cannot be extrapolated to estimate the burden of the drug resistance in the community. Secondly, there are very few accredited laboratories for second line of TB drugs in India and as such there can be problems about the interpretation and credibility of the profiles reported by many investigators. Nevertheless, one cannot ignore that the problem needs to be addressed by giving it due importance. However, this should not lead to scare as a very small proportion of MDR isolates has been generally found to be XDR. Many Institutions of Government of India including those of ICMR have been working hard to provide the services and augment the capabilities to accurately diagnose the resistance. Several international agencies are also playing their part. I am sure the infrastructure to accurately diagnose different types of the resistance to second line drugs and management of drug resistant cases will be strengthened over a period of time. Till then the readers should read these reports with caution knowing fully well the limitations but get ready to improve as per the needs to do better.

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