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Editorial

TUBERCULOSIS ASSOCIATED IMMUNE RECONSTITUTION INFLAMMATORY SYNDROME

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HIV substantially increases the risk of tuberculosis (TB) and it has become a major problem in controlling TB in many countries'. Sub-Saharan Africa is severely hit by the dual epidemic of HIV and TB with gradually increasing incidence of TB[1]. Often HIV is diagnosed while the test is requested as a part of evaluation of TB. Hence, worldwide a substantial proportion of patients being started on antiretroviral therapy (ART), particularly in sub-Saharan Africa, are also receiving anti-tuberculosis treatment (ATT). Though ART dramatically reduces TB risk by about 80%[2], high TB incidence rates have been noted in the first three months of ART in developing countries[3]. After initiating ART, all the components of immune system recover quantitatively and functionally, particularly CD4 count rises rapidly in the first month, representing redistribution of memory cells from sites of immune activation, followed by a more gradual recovery of nai've cells[4]. During the early period of rapid immune recovery, immune reconstitution inflammatory syndrome (IRIS) which is also known as immune recovery disease or immune restitution syndrome has come up as an important clinical entity complicating treatment of HIV-TB co-infection. IRIS is believed to result from dysregulated recovering immune responses, leading to exaggerated inflammation directed at the opportunistic pathogens[5]. IRIS is associated with certain infectious (e.g. mycobacteria, varicella zoster and cytomegalovirus) and non-infectious (autoimmune or neoplastic) conditions. In case of TB, two forms of IRIS are recognized[6]. Paradoxical TB-IRIS occurs in patients diagnosed with TB and started on ATT before ART, who then manifest with recurrent or new TB symptoms and signs after ART initiation. Unmasking TB-IRIS occurs in patients who are not on TB treatment when they start ART and who then have an abnormally heightened inflammatory presentation of TB usually within the first three months of ART.

Paradoxical reactions during ATT (new or recurrent TB symptoms or signs occurring after initial response to treatment) occur in patients irrespective of HIV infection or ART. Up to 25% of patients with TB lymphadenitis experience a paradoxical deterioration usually manifesting as enlargement of the existing nodes. Other manifestations include recurrent fevers, worsening pulmonary infiltrates, enlarging pleural effusions, development of tuberculous meningitis (TBM), new or enlarging tuberculomas or tuberculous lesions developing at other sites[7]. These paradoxical reactions are believed to reflect an immunologically mediated deterioration rather than ATT failure. The pathogenesis has variably been attributed to exposure and release of new antigen targets during mycobacterial killing and hypersensitivity to such antigens or exaggerated immune restoration with ATT[7].

Paradoxical reactions are far more severe and frequent in the period after ART initiation than those occurring in absence of HIV infection[13]. Paradoxical TB-IRIS occurs in 4.5-43% of patients starting ART while on ATT[8"18]. The median interval from ART initiation to onset of paradoxical TB-IRIS is two-four weeks[8"18] but cases may occur within a few days and rarely months after ART is initiated. The median duration of symptoms is two-three months[13,16]. Onset of the clinical manifestations of TB-associated IRIS should occur within the timeframe of three months for a diagnosis to be made[6]. The most frequent

clinical features are recurrent symptoms, fever, enlarging lymph nodes and new or enlarging serous effusions. Worsening of radiographic pulmonary infiltrate is seen in 45% TB patients starting ART[17]. Life-threatening manifestations of paradoxical TB-IRIS include new or recurrent meningitis, enlarging central nervous system tuberculomas, pericardial tamponade, acute renal failure, splenic rupture, intestinal perforation, airway compromise due to compression by enlarging nodes and respiratory failure. Overall, however, reports of death from paradoxical TB-IRIS are rare[14-19]. Although most of the cases are self-limiting, paradoxical TB-IRIS patients frequently require hospitalization involving diagnostic and therapeutic procedures resulting in considerable morbidity and burden on the health services. The most consistently identified risk factors for paradoxical TB-IRIS are disseminated TB, low CD4 count before ART and shorter ATT ART interval[18-19]. Paradoxical TB-IRIS is diagnosed based on characteristic clinical presentation, temporal relationship to the initiation of ART and exclusion of alternative explanations for clinical deterioration. It is very important to investigate for other opportunistic infections, TB treatment failure (e.g. due to non-adherence or drug resistance) or drug reaction. Consensus case definitions for use in resource-limited settings have recently been developed[6]. Mild cases require reassurance and symptomatic treatment. In more severe cases, non-steroidal anti-inflammatory drugs (NSAIDs) and corticosteroids have been effective. ART interruption should be considered in life-threatening cases (e.g. with severe CNS involvement).

High incidence rates of TB (5.6-23 per 100 person-years) in the first three months of ART have been reported mainly from developing counties[3]. The possible explanations are: patients may have sub-clinical TB that becomes clinically apparent on ART or be infected with TB around the time of ART initiation. The spectrum of clinical presentations may be sub-clinical, a typical clinical presentation or an exaggerated inflammatory presentation. Some authorities have regarded any presentation of TB diagnosed while patients are on ART as TB-IRIS provided there was a CD4 increase and viral load reduction. However, there is an increasing consensus that only a subset of these cases should be regarded as IRIS[6,21]. A nomenclature has been proposed and all TB diagnosed cases while on ART should be termed "ART-associated TB." The cases presenting with heightened intensity of clinical manifestations, particularly with a marked inflammatory component, during the first three months of ART, should be termed "unmasking TB-IRIS." Unmasking TB-IRIS is less well characterized than paradoxical TB-IRIS, with fewer cases reported but it may account for a proportion of the high mortality associated with TB diagnosed in the initial months of ART[3]. Further research to characterize the clinical manifestations and immunologic mechanisms of unmasking TB-IRIS will help in refining the proposed clinical case definition for this condition.

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Review Article

MULTIDRUG AND EXTENSIVELY DRUG-RESISTANT TB (M/XDR-TB): PROBLEMS AND SOLUTIONS*

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Summary: Multi Drug Resistant Tuberculosis (MDR-TB) and Extensively Drug Resistant Tuberculosis (XDR-TB) are posing a threat to the control of tuberculosis. The first WHO-IUATLD antituberculosis drug resistance surveillance carried out in 1994 in 35 countries reported the median prevalence of primary and acquired multi drug resistance as 1.4% and 13% respectively. Subsequently, second, third and fourth WHO-IUATLD global drug resistance surveillances were carried out in 1996-99, 1999-2002 and 2002-2007 respectively. Based on drug resistance information from 114 countries, the proportion of MDR-TB among all cases was estimated for countries with no survey information. It was estimated that 4,89,139 cases of MDR-TB emerged in 2006. China and India carry approximately 50% of the global burden. 35 countries and two Special Administrative Regions (SARs) reported data on XDR-TB for the first time in 2006. Multidrug and extensively drug-resistant TB 2010 Global report on Surveillance and response estimated that 4,40,000 cases of MDR-TB emerged globally in 2008 and caused an estimated 1,50,000 deaths. 9.4% of MDR-TB cases were found to have XDR-TB. To date, a cumulative total of 58 countries have confirmed at least one case of XDR-TB. M/XDR-TB is a man-made problem and its emergence can be prevented by prompt diagnosis and effective use of first line drugs in every new patient. The DOTS Plus proposed by WHO highlights the comprehensive management strategy to control MDR-TB. Laboratory services for adequate and timely diagnosis of M/XDR-TB must be strengthened and programmatic management of M/XDR-TB must be scaled up as per target set by global plan. Proper use of second-line drugs must be ensured to cure existing MDR-TB, to reduce its transmission and to prevent XDR-TB. Sound infection control measures to avoid further transmission of M XDR-TB and research towards development of new diagnostics, drugs and vaccines should be promoted to control M/XDR-TB. **[*Indian J Tuberc 2010; 57:180-191*]**

***Key words*:** Tuberculosis, Multi drug resistant tuberculosis, Extensively drug resistant tuberculosis

INTRODUCTION

Drug resistant tuberculosis has been reported since the early days of introduction of anti-TB chemotherapy, but Multi Drug Resistant Tuberculosis (MDR-TB) and more recently, Extensively Drug Resistant Tuberculosis (XDR-TB) have been areas of growing concern, and are posing a threat to global efforts of tuberculosis control. Prevalence of drug resistant TB mirrors the functional state and efficacy of tuberculosis control programmes and realistic attitude of the community towards implementation of such programmes[1]. Poor TB control generates MDR-TB and the misuse of second line drugs generates XDR-TB. More than 4,00,000 cases of MDR-TB emerge every year as a result of poor management of drug sensitive as well as drug resistant TB. DOTS Plus proposed by WHO highlighted the comprehensive management strategy to control MDR-TB. In 2006, XDR-TB was reported in all regions of the world and it has become a serious emerging threat to global public health, especially in countries with a high prevalence of Human Immunodeficiency Virus (HIV) infection. XDR-TB has raised the possibility that the current drug susceptible TB will be replaced with a form of TB with severely restricted treatment options. This would halt the progress made in recent years to control TB globally. The present write up reviews the present status of M/XDR-TB and how to prevent and control M/XDR-TB.

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* Updated based on the Dupont-IAT Oration delivered at the First International Conference of South East Asia Region (SEAR) and 63rd National Conference on TB and Chest Diseases – September, 2008 – Delhi.

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DEFINITION

Drug resistant tuberculosis is defined as a case of tuberculosis excreting bacilli resistant to one or more anti tubercular drugs. Multi Drug Resistant Tuberculosis (MDR-TB) is defined as disease due to *M.tuberculosis* that is resistant to Isoniazid (H) and Rifampicin (R) with or without resistance to other drugs. The term "Extensively Drug Resistant TB (XDR-TB)" is a new one which was provisionally defined as those persons with TB whose isolates were resistant to Isoniazid and Rifampicin and atleast three of the six main classes of Second Line Drugs(SLDs) (Aminoglycosides, Polypeptides, Fluoroquinolones, Thioamides, Cycloserine, and Para-aminosalicylic Acid) .But in October 2006, the World Health Organization revised the case definition of XDR-TB as TB with resistance to at least isoniazid and rifampicin as well as further resistance to a fluroquinolone and a second line injectable agent (kanamycin, amikacin or capreomycin).

TYPES OF DRUG RESISTANCE

Drug resistance may be of two types – Primary and Acquired. Primary drug resistance may be defined as drug resistance in a patient who has not received any anti tubercular treatment in the past. The resistance that develops in a patient who has received prior chemotherapy is defined as acquired drug resistance. Recently the terms "resistance in new cases" and "resistance in previously treated cases" have been proposed for use because of the difficulty to confirm the validity of the patients' past history of treatment. When one is not sure whether the resistance is primary or acquired due to concealed history of previous treatment or unawareness of treatment taken before, it is known as initial drug resistance. Thus initial resistance is primary resistance plus some undisclosed acquired resistance. Combined resistance is defined as the sum of primary and acquired resistance.

MDR-TB: GLOBAL

A review by WHO of a series of 63 surveys of drug resistant TB carried out between 1985–1994 led to the conclusion that the problem of drug resistance was global[2]. The overall percentages of resistance to different anti-tuberculosis drugs obtained from different surveys done throughout the world are shown in Tables 1 and 2. The rate of MDR-TB was very low in most of the surveys, ranging from 0-10.8% in the case of primary resistance and from 0 – 48% for acquired resistance. Multidrug resistance was reported to range from 0.5 – 14.3% in surveys where there was no distinction between primary and acquired resistance. In most regions of the world, the rates of MDR-TB were very low[2], except in New York and Nepal where high rates of acquired type MDR-TB were reported. It is evident that prevalence of drug resistant tuberculosis varied considerably throughout the world. The reasons for this variation in different surveys were the degree of selection of patient studied, the degree of misuse of drugs, the quality of enquiry regarding previous treatment and the inadequate culture and drug susceptibility facilities in many parts of the world.

First report of the WHO/IUATLD Global Project on Anti-Tuberculosis Drug Resistance Surveillance

Considering the limitation of the previous studies, a WHO/IUATLD global project of drug resistance surveillance spread over 35 countries in five continents was carried out between 1994-1997[2]. Median prevalence of primary and acquired multi-drug resistance was reported to be 1.4% (0-14.4%) and 13% (0 - 54.4%) respectively (Tables 1 and 2). Particularly, high prevalence of multi-drug resistance was found in the former Soviet Union, Asia, Argentina and the Dominican Republic. The WHO for the first time introduced the term MDR 'hotspot' where high prevalence of MDR has been observed. The 'hotspots' referred to the countries or regions where the combined prevalence of MDR TB exceeded 5%. The report concluded that resistance to anti-TB drugs was found in all 35 countries and regions surveyed, suggesting again that the problem was global.

Table 1: Global Primary/Initial drug Resistance

Study	*Any Drug*	*Any H %*	*Any S %*	*Any R %*	*Any E%*	*H+R%*
Cohn *et al*. review of 63 surveys(1985-1994)[2]	-	0 – 16.9	0.1 – 23.5	0 – 3.0	0 – 4.2	0 – 10.8
WHO-IUATLD 1994 – 1997 surveillance[3]	9.9(2.0-20.6)	7.3(1.5-31.7)	6.5(0.3-8.0)	1.8(0-16.8)	1.0(0-9.9)	1.4(0-17.1)
WHO-IUATLD 1996 – 1999 surveillance[6]	10.7(1.7-36.9)	6.2(0-28.1)	5.2(0.3-32.4)	1.2(0-15.8)	0.6(0-12.1)	1.0(0-14.2)
WHO-IUATLD 1999-2002 surveillance[11]	10.2 (0-57.1)	5.7(0-42.6)	6.3(0.5-7.5)	1.4(0-15.6)	0.8(0-24.8)	1.1[0-4.2]
WHO-IUATLD 2002-2007 surveillance[13]	17(0-56.3)	10.3(0-42.4)	10.9(0-51.5)	3.7(0-22.7)	2.5(0-21.8)	2.9(0-22.3)
M/XDR-TB Global report on surveillance and response 2010						0% – 28.3%

Table 2: Global Acquired drug Resistance

Study	*Any Drug*	*Any H %*	*Any S %*	*Any R %*	*Any E%*	*H/R%*
Cohn *et al*. review of 63 surveys (1985-1994)[2]	-	4 – 53.7	0 – 19.4	0 – 14.5	0 – 13.7	0 – 48.0
WHO-IUATLD 1994-1997 surveillance[3]	36.0(5.3-100.0)	-	-	-	-	13.0(0-54.4)
WHO-IUATLD 1996-1999 surveillance[6]	23.3(0.0-93.8)	19.6(0.0-0.0)	12.4(0.0-53.4)	12.0(0.0-50.0)	5.9(0.0-32.1)	9.3(0.0-48.2)
WHO-IUATLD 1999-2002 surveillance[11]	18.4 (0-82.1)	14.4(0-71.0)	11.4(0-71.1)	8.7(0-61.4)	3.5(0-54.2)	7.0(0-58.3)
WHO-IUATLD 2002-2007 surveillance[13]	35(0-85.9)	27.1(0-81.2)	20.1(0-83.5)	17.5(0-62.5)	10.3(0-54.3)	15.3(0-62.5)
M/XDR-TB Global report on surveillance and response 2010						0% – 61.6%

Table 3: Primary/Initial drug Resistance (India)

Study		*Total Prevalence*	*H%*	*S%*	*R%*	*H+R%*
ICMR (1968)[22]		20.1	11.7	12.	-	-
ICMR (1969)[23]		22	15.5	13.	-	-
Krishnaswamy KV *et al.* 1976[24]		-	10.6	9.5	-	-
Trivedi *et al* (1988)[2]		20	13.9	7.4	0	0
Chandrasekharan *et al* (1990)[25]		21.2	17.1	5.7	3	1.3
Chandrasekharan *et al* (1992)[27]	Rural	34.9	32.8	5.1	4.4	3.4
	Urban	20.5	17.3	4.1	2.9	1.4
Parmasivan *et al* (1993)[28]	North Arcot (1985-89)	25.0	13.0	4.0	2.0	1.6
	Pondicherry (1985-91)	13.9	6.0	4.0	0.9	0.7
Gupta *et al* (1993)[29]		19.5	10.1	7.6	3	0.7
Jain *et al* (1993)[30]		-	18.5	-	0.6	0.4
Jena *et al* (1996)[31]		7.9	2.9	4.9	1	0.1
Parmasivan *et al* (2000)[32] (Tamil Nadu)		18.8	15.1	6.8	4.4	3.1
R. Prasad *et al* (2001)[33]		27.4	15.6	11.	3.9	2.0
WHO-IUAT (1996-1999)[9]		18.8	15.4	6.8	4.4	3.4
Paramasivan *et al* (2002)[3]	North Arcot (South) 1999	27.7	23.4	12.	2.8	2.8
	Raichur (South) 1999-2000	21.9	18.7	7.2	2.5	2.5
WHO-IUATLD (1999-2002)[11]	Wardha	19.8	15.2	7.6	0.5	0.5
Sofia *et al* (2004)[35]	Bangalore City	27.7	13.7	22.	2.6	2.2
Mahadeo *et al.* (2005)[36]	Mayurbhanj 2000-2002	5.3	2.5	3.9	0.7	0.7
	Hoogli 2000-2001	16.7	10.3	13.	3.0	3.0
Zignol M *et al* (2006)[12]	-	-	-	-	-	2.4
WHO/IUATLD (2002-2007)[13]		-	11.71	9.9	2.2	2.8
MXDR-TB Global report on surveillance and response 2010						2.3

Table 4: Acquired drug Resistance (India)

Study	*Total Prevalence %*	*H %*	*S %*	*R %*	*H+R %*
ICMR (1969)[25]	32 (22-74)	15-69	12-63	-	-
Trivedi *et al* (1988)[24]					
1980	50.1	34.5	26	2.8	95% of R resistant were resistant to H or S or both
1986	65.3	55.8	-	37.3	-
Dutta M *et al.* 1993[37]	-	7.0	26.0	12.0	6.0
Jain *et al* (1992)[10] Delhi	50.7	50.7	-	33.3	33.3
outside Delhi	78.8	78.8	-	61.5	61.5
Chowgule *et al* (1998)[38]	25.6	15	53.6	66.8	10.7
WHO-IUATLD Surveillance (1994-1997)[3]	32.4	28.8	18.1	11	13.3
WHO-IUATLD Surveillance (1999-2002)[6]	50.0	50.0	12.5	25.0	25.0
Shah AR *et al* (2002)[39]	58.67	57.18	35.58	37.17	35.1
Deivanayagam.(2002) [C]	71.0	66.3	35.6	55.5	54. 8
Paramasivan *et al* (2002)[34]					
North Arcot (South)	81.0	81.0	56.2	69.0	69.0
Raichur (South)	100.0	100.0	36.4	100.0	100.0
R. Prasad *et al* (2003)	79.2	48.6	36.6	34.4	29.5
Zignol M, *et al* (2006)[12]	-	-	-	-	14.7
WHO-IUATLD (2002-2007) surveillance[13]	-	36.8	26.2	18.1	17.2
M/XDR-TB Global report on surveillance and response 2010					17.2

Second report of the WHO/IUATLD Global Project on Anti-Tuberculosis Drug Resistance Surveillance

A second WHO/IUATLD global project on drug resistance surveillance in 58 countries / geographical sites was carried out in 1996-1999[4] Trends of drug resistance were also observed from 28 sites. Median prevalence of primary and acquired multidrug resistance was reported in 1% (0-14%) and 9% (0-48%) respectively. Of the 58 sites surveyed, drug resistance among new and previously treated cases were reported in 54 and 48 sites respectively. Most of the previous 'hotspots' of MDR-TB were confirmed again; however new areas in Russia and China were added.This global survey tested a total of 61,415 patients with tuberculosis (Median per site 661; range 11-12675). These sites accounted for 610,000(18%) of 3.3 million cases of tuberculosis reported to WHO in 1997 and 1.5 billion (26%) of the world's 5.8 billion inhabitants. Several countries including 11 of the 22 world tuberculosis high burdened countries had not yet been surveyed. A mathematical model had estimated

the magnitude of MDR-TB worldwide and suggested that in year 2000, 3% (273,000 ; 95% CI, 185,000–414,000)of all new and previously treated TB cases were MDR-TB.[5] The trend analysis confirmed that MDR TB was not a major problem in countries implementing TB control according to international guidelines for several years. Botswana, Chile, Cuba & Czech Republic and Uruguay have all shown very low prevalence of MDR TB confirming that efficient TB control prevents the outset and spread of MDR TB[6–9].

Third report of the WHO/IUATLD Global Project on Anti-Tuberculosis Drug Resistance Surveillance

A Third WHO/IUATLD global project on drug resistance surveillance in 77 countries/ geographical sites was carried out in 1999–2002 [11], representing 20% of the global total of new smear positive TB cases. It includec 39 settings not previously included in Global Project and reported trends for 46 settings. Median prevalence of primary and acquired multidrug resistance was reported in 1.1% (0–14.2%) and 7% (0–58.3%) respectively (Tables 1 and 2). This report analyzed the distribution of MDR Prevalence (among new cases) from 74 settings. After analysis, the cut-off value for hot spots was reset to MDR prevalence of more than 6.5% among new cases. There were 10 countries regarded as hot spots with MDR-TB prevalence viz. Ecuador (6.6%), Henan (7.8%), Latvia (9.3%), Lithuania (9.4%), Liaoning (10.4%), Estonia (12.2%), Uzbekistan (13.2%), Tomsk Oblast (13.7%), Israel (14.2%) and Kazakhastan (14.2%). Despite the expansion in coverage of drug-resistance surveillance for both new and previously treated cases in recent years, data on drug resistance are still not available for more than 100 countries. To estimate the levels of drug resistance in places where direct data are not available, Zignol *et al*,[12] had developed statistical models for settings where data were available and applied them to places where they are not. After their analysis, they have revealed the total number of MDR-TB cases estimated to have occurred worldwide in 2004 is 424,203 (95% CI, 376,019–620,061), or 4.3% (95% CI, 3.8%–6.1%) of all new and previously treated TB cases. Three countries—China, India, and the Russian Federation—accounted for 62% of the estimated global burden. In the same year, the total number of MDR –TB cases was 2.7%(95%CI,2.4%–3.8%) of new cases and 18.4% (95%CI,14.2%–31.7%) of previously treated cases. This study provides a new comprehensive set of estimates of the incidence of MDR-TB in 184 countries and globally. They have found lower rates of MDR-TB in countries of Central Europe such as Hungary, Macedonia and Turkey in comparison to previous studies. Their study showed a positive correlation between proportion of patients who had previously received treatment and proportion of MDR-TB cases among new cases.

Fourth report of the WHO/IUATLD Global Project on Anti-Tuberculosis Drug Resistance Surveillance

A Fourth WHO/IUATLD global project on drug resistance surveillance included drug susceptibility test results (DST) from 91,577 patients from 93 settings in 81 countries and two SARs of China collected between 2002 and 2007,and representing 35% of the global total of notified new smear-positive TB cases [13]. It included data from 33 countries that have never been previously reported. New data were included from the high TB burden countries like India, China, Russian Federation, Indonesia, Ethiopia, Philippines, Vietnam, Thailand and Myanmar. Between 1994 and 2007, a total of 138 settings in 114 countries and 2 SARs of China had reported data to the global project. The median prevalence of primary and acquired MDR-TB globally was 2.9% (2.2–3.6%) and 15.3% (9.6–21.1%) respectively. The global population weighted proportion of multi drug resistance among all TB cases was 5.3% (95%CI, 3.9–6.6%). It is estimated that 489,139 MDR TB cases emerged in 2006 globally and the global proportion of multidrug resistance among all new and previously treated cases was 4.8% . China and India carry approximately 50% of the global burden and Russia a further 7%. Multidrug and Extensively Drug-Resistant TB (M/XDR-TB) 2010 Global report on Surveillance and response, estimated 3,90,000–5,10,000 cases of MDRTB

emerged globally in 2008 (best estimate, 4,40,000 cases). Among all incident TB cases globally, 3.6% (95% CI. 3.0—4.4) were estimated to have MDR-TB, These estimates, which lie in the same range as the previous ones, were based on more data and revised methodology. MDR-TB caused an estimated 1,50,000 deaths globally in 2008[14].

XDR-TB: GLOBAL

Although limited data exist in the literature about Extensively Drug-Resistant Tuberculosis (XDR-TB) and second-line–drug resistance patterns among MDR TB patients, yet Centers for Disease Control and Prevention, USA surveyed the Network of Supranational Reference Laboratories for *M. tuberculosis* isolates that were resistant to second-line anti-TB drugs during 2000–2004[15]. They have defined Extensively Drug-Resistant TB (XDR TB) as MDR TB with further resistance to three of the six classes of second-line drugs. Of 23 eligible laboratories, 14 (61%) contributed data on 17,690 isolates, which reflected drug susceptibility results from 48 countries. Of 3,520 (19.9%) MDR TB isolates, 347 (9.9%) met criteria for XDR TB. Among XDR TB patients, combination drug-resistance patterns included 90 (3.4%) with resistance to aminoglycosides, capreomycin and fluoroquinolones; 102 (3.4%) with resistance to aminoglycosides, fluoroquinolones, and thioamides; and 94 (3.8%) with resistance to fluoroquinolones, thioamides, and para-aminosalicylic acid. Nearly half (n – 167. 48.1%) of all XDR TB isolates were resistant to all four first line drugs, bringing the total to >7 drugs to which the isolate was resistant. Among the group of industrialized nations, 53 (6.5%) MDR TB patients met criteria for XDR TB. Among patients from Russia and Eastern Europe, 55 (13.6%) MDR TB patients met criteria for XDR TB. Among patients from the Republic of Korea, 200 (15.4%) MDR TB patients, who accounted for 1.1% of all *M. tuberculosis* isolates tested, met criteria for XDR TB. Data from patients undergoing retreatment for TB in Hong Kong showed that 30 (17%) MDR TB isolates were resistant to >3 second-line drugs, thereby meeting criteria for XDR TB[16]. A drug-resistance survey of 477 culture-positive new patients and patients undergoing retreatment in Abkhazia, Republic of Georgia, found that of 63 MDR TB patients, two (3%) had additional resistance to three second-line drug classes, consistent with XDR TB[17]. More recently, clusters of XDR TB have been reported in South Africa and Iran[18,19] and have been associated with HIV infection and rapid and high death rates. In the Fourth WHO/IUATLD anti-TB drug resistance surveillance report, thirty five countries and two SARs have reported data on XDR-TB. The Quality assurance for laboratory testing was variable among countries reported. Out of total 4012 MDR-TB cases, 307 (7%) were XDR-TB cases[3].In general, absolute numbers of XDR-TB cases were low in Central and western Europe, the Americas and in the Asian countries that reported data. The XDR-TB proportion among MDR-TB in these settings varied from 0% in 11 countries to 30% in Japan. These countries have a relatively low MDR-TB burden, so this represents a few absolute cases. A more significant problem lies in the countries of the former Soviet Union. Of the nine countries that reported, approximately 10% of all MDR-TB cases were XDR ranging from 4.0% in Armenia to almost 24.0% in Estonia; however these proportions represent a much larger absolute number of cases. In a study conducted in Lima, Peru on 810 patients referred for individualized antituberculous drug therapy from 1999–2002,48(7.4%) patients of total 651 patients tested had XDR-TB, and the remaining 603 were all MDR-TB[20].Recently released data from South Africa showed that 5.6% of 17,615 MDR isolates collected from 2004 to October 2007 were XDR-TB. Proportions varied across provinces with Kwa Zulu-Natal reporting 14% of 4701 MDR cases as XDR-TB. Selection and testing practices varied across the country and over time; however all isolates correspond to individual cases[21]. As of January 2010, a cumulative total of 58 countries have confirmed at least one case of XDR-TB. 5.4% of MDR-TB cases were found to have XDR-TB globally[2].

MDR-TB: INDIA

Development of drug resistance in India was noted since the beginning of the chemotherapeutic era. Indian Council of Medical Research (ICMR)

conducted two surveys in 1965-67 to estimate the prevalence of drug resistance[22,23]. Since then several studies have been conducted in different parts of the country. Multi-drug resistance among new cases varied between 0-5%[24-26]. A study conducted by Tuberculosis Research Centre, Chennai in collaboration with the National Tuberculosis Institute, Bangalore using WHO/IUATLD guidelines between 1999-2002 including six districts in India showed that primary MDR-TB ranged from 0.7-2.8%[34-35]. The overall impression as seen in Table 3 is that the primary MDR-TB has remained more or less constant over the years. According to the third Global Report of WHO, prevalence of MDR-TB among new cases in India (Wardha) was 0.5 %[1].

The prevalence of acquired multi drug resistance rates also varied from 6 - 100%[3,24,37-47] (Table 4)in the same time period. In a study conducted in Gujarat, it was found that 95% of the R resistant strains were also resistant to H or S or both. The WHO - IUATLD surveillance[3] in India reported the combined prevalence of MDR-TB to be 13.3% (95%CI, 10.9 - 14.9%) in 1998, however, this was done on a small sample of 2240 people around Delhi city and therefore was not representative of the country[3]. The WHO - IUATLD global drug resistance surveillance carried out between 1996-1999 reported that the median prevalence of primary and acquired MDR-TB to be 3.4% (95%CI, 1.8-5.1%) and 25% (95%CI, 7.3-52.3%) respectively.[4]. Zignol *et al* estimated the incidence of primary and acquired MDR-TB cases to be 2.4% (95% CI,1%-5%) and 14.7% (95% CI, 2.1%-56.9%) respectively. The estimated incidence of MDR-TB among new and previously treated cases was 1.1% of all the TB cases in India[12].The Fourth global surveillance of WHO-IUATLD, carried out in 2002-2007 also reported new data from Gujarat giving the first reliable source of data with regard to MDR-TB among previously treated cases in India . Data from nine sites in India show that drug resistance among new cases is relatively low; however, new data from Gujarat indicate that 17.2% MDR-TB among retreatment cases is higher than previously anticipated and it is estimated that 1,10,132 (95% CI, 79,975-142,386) MDR-TB cases emerged in India in 2006, representing over 20% of the global burden.. The estimated prevalence of MDR-TB among all TB cases was 4.9%(95%CI, 3.9-6.2%)[48]. M/XDR-TB 2010 Global report on surveillance and response estimated MDR-TB among new TB cases as 2.3% (1.8-2.8%), and in previously treated patients as 17.2% (14.9-19.5%). It is estimated that 99,000 cases of MDR-TB (95 % CI 79000-120000) emerged in India in 2008.

XDR-TB: INDIA

Although isolated reports, both published and unpublished indicate the existence of XDR-TB in the country, it is not possible as yet to estimate its magnitude and distribution from the available data. Drug Susceptibility Test (DST) results of Second line anti-tuberculous drugs should be interpreted with great caution due to limited capacity of laboratories, absence of quality-assurance and lack of standardized methodology. According to the data reported on XDR-TB from India, it varied from 1.5% to 11%,[42-45] of MDR-TB, Multidrug and Extensively Drug-Resistant TB (M/XDR-TB) 2010 Global report on Surveillance and response estimated prevalence of XDR among MDR-TB patients as 3.2 %(95% CI, 1.2-6.6%)[14]

RISK FACTORS OF M/XDR-TB

Several risk factors have been identified in the causation of drug resistant tuberculosis of which the three most important are-previous treatment with anti-tubercular drugs which may be inappropriate, incomplete or erratic, high prevalence of drug resistant tuberculosis in the community and contact with a patient known to have drug resistant tuberculosis. In patients with previous treatment or disease, the odds of resistant tuberculosis were 4-7 times higher than for persons with no history of past treatment. However standardized short course chemotherapy carries only a minimal risk of emergence of MDR-TB[46]. Other factors that may be responsible for increased risk of resistant tuberculosis are - co-infection with HIV, socioeconomically deprived groups in slums, prisons, correctional facilities, day care centres, intravenous

drug abusers and other immunocompromised states as in transplant recipients, anti cancer therapy patients, and patients with diabetes mellitus. Radiologically far advanced pulmonary tuberculosis with cavitary lesions were four times as likely to harbour drug resistant organisms. Mismanagement of MDR-TB with erratic use of Second Line Drugs may lead to development of XDR-TB[47].

SOURCES AND CAUSES OF M/XDR-TB

Though unfortunate, yet a reality is that M/XDR-TB is a man-made problem. Drug Resistant Tuberculosis results largely from poorly managed case of TB.[48] If first line Anti-TB drugs are misused, MDR-TB can develop and if second line Anti-TB drugs are also misused, then XDR-TB can develop. The sources are many and the causes multi-factorial. To blame for this are governments, the pharmaceutical industry, doctors, patients and their families, each of whom contribute in their own way to add up to the problem. Many governments in the world play their share by providing poor infrastructure in the tuberculosis control programmes, unnecessary administrative control on purchase and distribution of drugs with no proper mechanism on quality control and bioavailability tests. However, it may be noted that RNTCP in India has been able to address these issues.The pharmaceutical industry in its turn contributes by manufacturing drugs of uncertain bio-availability in fixed dose or inappropriate drug combinations, poor storage condition of drugs and substitution by inferior quality drugs by pharmacies. The doctor, by his lack of knowledge regarding doses, duration of treatment, side effects and standard regimens, frequent change of brand names and poor patient motivation, contributes the lion's share to the problem. In a study where prescriptions of 749 doctors,majority being from private health sector, were analyzed , 75% of the doctors were found to have made some prescription error [49] that may lead to the genesis of M/XDR-TB , Added to this is the poor teaching and training facilities for them. Philip C Hopewell *et al* had notec that stucies of the performance of the private sector in different parts of the world suggest that poor quality care is common. Clinicians in particular those who work in the private health-care sector make mistakes like use of non-recommended drug regimens with incorrect combinations of drugs, mistakes in both drug dose and duration of treatment, and failure to supervise and assure adherence to treatment.[50] Non-compliant patients due to monetary lack, lack of information, side effects of drugs and social myths and misconceptions often do not adhere to treatment. Co-morbid conditions like diabetes, HIV, psychiatric conditions, the habits of smoking and alcoholism make the patient more vulnerable. To sum up, M/XDR-TB usually results from inadequate drug therapy in multibacillary cases of tuberculosis, addition of single drug in cases of failure, difficulty in obtaining drugs by the poor due to lack of financial resources or social insurances, frequent shortage of second line anti-tuberculous drugs by poor management and or financial constrains, use of drugs or combination of drugs (FDC) with unproven bioavailability, lack of motivation at the beginning of treatment and inadequate self administration of drugs without direct observation.

PREVENTION AND CONTROL OF M/XDR-TB

The primary aim in the control of multi-drug resistant and extensively drug resistant tuberculosis is to prevent its development in the first place. This can be done by Directly Observed Treatment Short Course (DOTS), which is the most cost effective way of treatment and prevention of MDR-TB A. the same time since M/XDR-TB cases respond poorly to short course chemotherapy, careful introduction of second line drugs to treat M/XDR-TB cases to reduce further transmission of such strains will be required.[51] To control the emergence of MDR-TB, WHO in 1998 had proposed the work plan known as 'Dots Plus' for which WHO had established Green light committee[52]. The primary aims of committee were to approve, conduct and oversee pilot projects based on guidelines for establishing 'Dots Plus' pilot projects. 'Dots Plus' is a comprehensive management strategy to control MDR-TB. Following the roll out and successful implementation of "DOTS-Plus" pilot projects for the management of MDR- TB between 2000 and 2005, a new Stop TB

Strategy was launched in 2006. The New Stop TB Strategy includes the diagnosis and the management of MDR-TB.[52] The launch of the Stop TB Strategy was followed by the Global Plan to Stop TB, 2006-2015 that provided targets for scale up and budgets required for the implementation of the strategy Stop TB partnership.[54] The terminology DOTS Plus has now been replaced by Programmatic Management of Drug Resistant cases (PMDT).

To combat the threat of XDR-TB, WHO convened a Global Task Force on XDR-TB in October 2006 and recommended to strengthen basic activities to control TB and HIV/AIDS, to avoid additional emergence of M/XDR-TB as well as acceleration of treatment of MDR and XDR-TB cases with universal access to sound management of M/XDR-TB by 2015 in all countries and near to universal access in the high burden countries by 2010.[55] The revised plan recommended the treatment of 1.6 million M/XDR-TB cases by 2015 instead of 8,00,000 MDR-TB cases. It will require integration of M/XDR-TB activities into general TB control activities. It will include the strengthening of laboratory services for adequate and timely diagnosis of M/XDR-TB, surveillance of M/XDR-TB, development and implementation of sound TB infection control policies, Advocacy Communication and Social Mobilization to sustain political commitment and resource mobilization and the promotion of research and development into new diagnostics, drugs, vaccines and operational research on MDR-TB management. It is expected that full implementation of this response plan will save the lives of thousands of people infected by M/XDR-TB and will be able to prevent and control M/XDR-TB.

CONCLUSION

M/XDR-TB is a man-made problem and posing threat to control of TB .It is estimated that more than 4,00,000 cases of MDR-TB emerge every year globally as a result of poor management of sensitive as well as drug resistant TB cases. PMDT proposed by WHO highlights the comprehensive management strategy to control MDR-TB. Laboratory services for adequate and timely diagnosis of M/XDR-TB must be strengthened to fill up the gap betwwen vision and actual implementation and programmatic management of M/XDR-TB must be scaled up as per target set by global plan. It must be emphasized that optimal treatment of MDR-TB alone will not curb the epidemic. Efforts must be focused on the effective use of first line drugs in every new patient so as to prevent the ultimate emergence of multidrug resistance. Availability of good quality second-line drugs and their proper use must be ensured to cure existing MDR-TB, to reduce transmission of MDR-TB and to prevent XDR-TB. Sound infection control measures to avoid further transmission of M/XDR-TB and research towards development of new diagnostics, drugs and vaccines should be promoted to control M/XDR-TB.

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Original Article

TUBERCULOSIS AMONG HEALTH CARE WORKERS IN A TERTIARY CARE INSTITUTE FOR RESPIRATORY DISEASES IN NEW DELHI

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Summary

Background: LRS Institute of Tuberculosis and Respiratory Diseases, a tertiary care pulmonary institute in Delhi, India.

Aims: To find out the risk of tuberculosis disease among health care workers (HCWs) of LRS Institute.

Methods: Retrospective study, where all members of the staff working in this hospital were interviewed regarding development of tuberculosis after joining this institute.

Results: A total of 40 cases of tuberculosis were reported by the health care workers between March 1999 to March 2008 yielding an overall risk of 727 per 1,00,000 population per year which is four times higher than the reported national average. Among these 40 cases, 25 (62.5%) were pulmonary and 15 (37.5%) were extra-pulmonary tuberculosis.

Conclusion: This institute's health care workers have to deal with a large number of tuberculosis patients, the risk of exposure is more in them and thus having the disease. Multi-centric studies are needed to evaluate the true prevalence of tuberculosis among HCWs and effective intervention strategies are required to reduce nosocomial transmission. **[*Indian J Tuberc 2010; 57:* 192-198]**

Key words: Tuberculosis, Health care workers, Nosocomial tuberculosis

INTRODUCTION

The disease 'Tuberculosis' (TB) affects almost one third of world's population and eventually these patients present to health care workers (HCW) who participate in active management and thus become specially vulnerable to exposure and infection[1]. A systemic review found incidence of tuberculosis among HCWs to range from 69 to 5780 per 100,000 per year in low and middle income countries[2]. The level of risk varies by hospital setting, occupation and infection control measures[3-5]. A hierarchy of control measures, including administrative, engineering and environmental controls and personal protection measures, has been recommended to reduce nosocomial TB risk[6,7] but difficult to implement in resource poor countries. Several factors like the overwhelming number of TB patients and repeated exposures to smear-positive TB patients, lack of infection control procedures, etc. may facilitate nosocomial transmission in Indian hospitals, although their relative importance in facilitating transmission is unknown[8]. India has more TB patients than any other country[9] and accounts for one fifth of the world's incident TB cases[10]. Every year, TB develops in nearly two million persons in India, and nearly one million cases are smear positives; an estimated 40% of the Indian population is latently infected with *M. tuberculosis*[9]. Despite the high prevalence of TB in India and the expected high probability of nosocomial transmission, little is known about nosocomial TB. Few available studies from India suggest a very high incidence of both latent and active tuberculosis among health care workers[11-14].

The present study was undertaken to evaluate the risk of tuberculosis disease among health care workers working at a tertiary level respiratory diseases institute in north India, the Lala Ram Swaroop Institute of Tuberculosis and Respiratory Diseases (LRS institute of TB and RD).

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METHODOLOGY

This study was done in LRS Institute of TB and RD. All members of the staff working in this institution were included in the study. Data were collected in the months of May and June, 2008. Information was obtained from all health care workers, using a semi-structured interview schedule, after obtaining informed consent. The questionnaire had items on demography, category of staff, total duration of service at the hospital and history of TB before and after joining the hospital, co-morbid illnesses and concomitant drug treatment. Occurrence of TB was defined when the study participants reported being diagnosed as having tuberculosis by a qualified doctor. The risk of tuberculosis only for the last ten years (March 1999-March 2008) was calculated. For presence of BCG scar, first left upper arm was inspected by a trained health worker. If no scar was found, then the right arm was also inspected for presence of any scar.

No additional investigation or screening was performed in any of the study participants, and no further attempts were made to verify any aspect of information provided by the respondents. All information gathered was confidential.

As the number of the staff varied in different years also in different times of the same year, to calculate mean number of staff, the staff position as on 31st of March of each year was taken into consideration.

Risk of tuberculosis disease was calculated by dividing number of staff who were affected by total number of eligible staff. The duration of stay in the hospital for all the staff were summed up and risk was expressed as number of tuberculosis cases per 100,000 HCWs per year. The cumulative incidence (person-years) was calculated over 10 years taking mean number of workers into consideration.

To find out risk of tuberculosis disease among different categories of staff, we divided the staff among some broad categories like doctors, nurses, paramedical staff, (lab technicians, other technicians, pharmacists, health workers, project staff), administrative staff and class IV staff (including ward boys, peon, ayah and other workers employed on daily wage basis).

The study protocol was approved by the Institute's Ethics Committee.

Analysis

Data were entered in MS-Excel sheet and analysis was done using SPSS-12. To find out association between two variables, chi-square test was computed.

RESULTS

A total of 550 staff participated in the current study. Mean number of total workers in LRS in last 10 years (1999-2008) was 556. So the response rate was 99% as six (1%) participants refused to give consent.

Baseline characteristics of the staff (Table-1)

The mean age of the study participants was 39.13 ± 9 Yrs, minimum age being 18 years and maximum age was 60 years. Forty-two per cent of the study participants were in the age group of 31-40 years. Fifty-nine per cent of the participants were males and 79% were Hindus. Mean years of work in the institute was 4.15 ± 3 yrs, the minimum being eight months and maximum being 30 years. Forty one per cent of the workers have worked in the institute for 49-72 months.

Eighty-six per cent of the workers were married and 62% belonged to nuclear family. Thirty-one per cent of the workers were present smokers and sixty-seven per cent were non-smokers (have not ever smoked cigarettes/bidis on a regular basis). Six per cent of the study participants had a family history of tuberculosis and 2% of the population in this study had a past history of tuberculosis. Sixty-six percent of the study participants had presence of a BCG scar. Twelve percent of the study participants were doctors and 27% were nurses. Class-IV staff constituted 46% of the study population.

Table 1: Baseline characteristics of the participants(N=550)

Age (years) (N=550)	Number	Percentage
18–30	104	19
31–40	232	42
41–50	152	28
51–60	62	11
Gender (N=550)		
Male	324	59
Female	226	41
Religion (N=550)		
Hindu	433	79
Muslim	89	16
Christian	20	4
Others	8	1
Years of service (months) (N=550)		
0–24	162	29
25–48	148	27
49–72	223	41
>72	17	3
Income (rupees) (N=550)		
=<10,000	262	48
11–20000	175	32
21–30000	69	13
31–40000	18	3
41–50000	14	2
>50000	12	2
Marital Status (N=544)		
Married	473	86
Un-married/single	71	13
Smoker (N=513)		
Present smoker	160	31
Non-smoker	341	67
Ex-smoker	12	2
Family Type (N=550)		
Nuclear	339	62
Joint	211	38
Presence of BCG scar (N=545)	363	67
Family History of TB: Yes (N=545)	31	6
Past History of TB : Yes (N=545)	9	2
Different categories of staff (N=550)		
Doctors	65	12
Nurses	147	27
Paramedical workers	45	8
Administrative staff	39	7
Class-IV staff	254	46

Risk of tuberculosis in Health Care Workers (Table-2)

A total of 40 cases of tuberculosis were reported by the health care workers between March 1999 to March 2008. Out of these 40 cases, 25 (62.5%) were pulmonary and 15 (37.5%) were extra-pulmonary tuberculosis. Four cases were reported among doctors, eight cases among nurses, four cases among paramedical workers, two cases among administrative staff and 22 cases among different class IV staff.

As the response rate was 98-99%, to calculate risk of tuberculosis, the number of workers who had participated in the study was considered. The overall risk of tuberculosis among HCWs was 727 per 1,00,000 population per year. For doctors, the risk was 651 per 1,00,000 per year, for nurses 544 per 1,00,000 per year, for paramedicals 889 per 1,00,000 per year, for administrative staff 512 and for class IV staff 866 per 1,00,000 per year.

Variables associated with reported tuberculosis cases (Table-3)

We found that the number of tuberculosis cases had increased with increase in the age (current) of the HCW. Two percent of the HCWs in the age group of 18-30 years , 7% in the age group of 31-40 years and 13% in the age group of 41-50 years reported as having tuberculosis after joining the institute and this difference was statistically significant. However, only 3% of the workers in the age group 51-60 years reported to have been affected by tuberculosis. Eight per cent of the male employees and six percent of the female employees reported as having tuberculosis.

We could not find any statistically significant difference between reported tuberculosis and religion of the employee, family type, total income, smoking status, presence of BCG scar, etc. Though the number of reported tuberculosis cases increased with years of service, as it was 4% for those who have worked for 24 months, 8% for those who have worked for 48 months and 9% for those who have worked for 72 months, the differences were not statistically significant.

More number of reported tuberculosis cases were found among paramedical workers and class IV staff (9% each) compared to nurses and administrative staff (5% each) and doctors (6%). But this difference was not statistically significant.

Table 2: Risk of tuberculosis among different categories of health care workers.

Category of staff (N=40)	Total no of tuberculosis cases	Risk of tuberculosis (per 1,00,000 population per year)
Administrative staff	2	513
Nurses	8	544
Doctors	4	615
Class IV staff	22	866
Paramedicals	4	889
All Health care workers	40	727

Table 3: Variables associated with risk of tuberculosis disease

Age (years) (N=40)	Number of HCWs who developed tuberculosis	Percentage	Chi-square and P value
18-30	2	2	13.77 & **0.003**
31-40	16	7	
41-50	20	13	
51-60	2	3	
Gender (N=40)			
Male	26	8	0.66 & 0.72
Female	14	6	
Religion (N=40)			
Hindu	34	8	2.08 & 0.55
Muslim	4	**4**	
Christian	2	10	
Others	0	0	
Years of service (months) (N=40)			
0-24	7	2	5.1 & 0.165
25-48	12	8	
49-72	21	9	
>72	0	0	
Income (rupees) (N=40)			
=<10,000	20	8	3.39 & 0.639
11-20000	9	5	
21-30000	6	9	
31-40000	2	11	
41-50000	1	**7**	
>50000	2	**17**	
Smoker (N=513)			
Present smoker	13	8	
Non-smoker	22	6	1.379 & 0.502
Ex-smoker	0	0	
Family Type (N=40)			
Nuclear	27	8	.627 & 0.269
Joint	13	6	
Presence of BCG scar (N=545)			
Yes	25	7	0.327 & 0.567
No	15	8	
Different categories of staff (N=40)			
Doctors **(N=40)**	4	6	2.018 & 0.73
Nurses	8	5	
Paramedical workers	4	9	
Administrative staff	2	5	
Class-IV staff	22	9	

None of the health care workers who had reported having tuberculosis had past history or family history of tuberculosis or other associated risk factors like on immunosuppressant drugs or other co-morbid conditions.

DISCUSSION

India has a long history in TB research but nosocomial tuberculosis at large has been neglected by the researchers. Although a few studies have been published[6, 11-14], many more are needed. There is currently no assessment of occupational risk of tuberculosis among health care workers.

This study has yielded a figure of 727 cases per 1,00,000 health care workers per year which is four times more than the reported incidence in general population (168 per 100,0000 population)[15].

We calculated risk of tuberculosis in person-years to adjust the variable duration of stay of the health care workers in the institute.

Pai *et al* at a rural medical school hospital in Sevagram, performed the tuberculin skin test (TST) and a whole-blood interferon-γ release assay (IGRA) for 726 healthcare workers. They found 50% of the HCW were positive for tuberculosis infection by tuberculin sensitivity test[11]. They also did a repeat survey of 216 medical and nursing students in this cohort. When both tests were used, the annual risk of latent TB infection was estimated to be 5% [11]. The estimated community-based annual risk of infection in India is 1.5%[16], and therefore the excess risk of 3.5% may be attributable to nosocomial exposure[8].

In a retrospective review of health care workers who underwent anti-TB treatment in a tertiary care hospital in Vellore, Gopinath *et al* [6] identified 125 health care workers who had been treated for active TB between 1992 and 2001. They found overall incidence of sputum positive cases was similar to that observed in the general population. However, these rates may have been underestimated because only health care workers who underwent TB treatment in that hospital were counted.

At a tertiary care hospital in Chandigarh, Rao *et al*[12] estimated the incidence of active TB among resident physicians. Among residents already working in the hospital, TB developed in 9 (2%) of 470, for an incidence of 11.2 new cases per 1,000 person-years of exposure.

Risk of tuberculosis found in this study is much lower than reported by Rao *et al* [12]. This might be due to the fact that this institute being a known hospital for pulmonary diseases, health care workers are trained to take personal protective measures. Also health education messages are regularly disseminated by health workers to patients both at out and in patients' departments.

In this study, we have found that 37% of the health care workers had extra-pulmonary form of tuberculosis. This is more than the reported 18% of patients on directly observed treatment under the Revised National Tuberculosis Control Programme[1] but less than the figure (57% and 43%) reported by Rao *et al*[12] and Gopinath *et al*[6].

Pai *et al* reported that increasing age of the employees and duration of employment were risk factors for latent TB infection. We also found that the number of tuberculosis cases had increased with increasing age (current) of the employee and it was statistically significant.

We found reported number of tuberculosis, higher among paramedical and class IV staff than nurses and doctors which highlights the need for further studies, including other variables like socio-economic, nutritional status, co-morbid conditions and awareness about the disease. This finding also stresses upon the fact of the need for dissemination of health education messages and conducting a study on use of protective measures by different categories of health care workers.

We acknowledge certain limitations of this study. Firstly, we are reporting the incidence of tuberculosis based on the report of the health care workers and it was not cross-checked with any other medical and laboratory reports. The disease having a social stigma, increases the chance of

under-reporting despite ensuring confidentiality. Secondly, the variable duration of stay of the health care workers in the institute also might have affected study results. A little more than half (56%) of the study population have worked for –< 4 years in the institute. So, we may not have data on some workers who might have got the infection while working in the institute but have developed the disease at a later stage.

In conclusion, as Indian health care workers have to deal with a large number of tuberculosis patients, they are more at risk of exposure and thus having the disease. More studies are needed to evaluate the true prevalence of tuberculosis among HCWs and to evaluate the risk factors for nosocomial tuberculosis. Also we need studies on effective intervention strategies to reduce nosocomial transmission in India, being a resource poor country.

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PRIVATE PRACTITIONERS' KNOWLEDGE, ATTITUDE AND PRACTICES ABOUT TUBERCULOSIS, HOOGHLY DISTRICT, INDIA

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Summary

Setting: Allopathic private practitioners (PPs) in Hooghly district, West Bengal, India

Objectives: To assess knowledge, attitudes and practices of PPs about diagnosis and management of TB patients and Revised National TB Control Programme (RNTCP) and their involvement in the programme.

Methods: We randomly selected 260 PPs. Using a self-administered, pre-tested questionnaire, we collected information about investigations prescribed for diagnosis of TB, treatment regimens used, and health education given to TB patients. We collected information about their involvement in RNTCP and reasons for non-involvement.

Results: Only 29 (11%) PPs were involved in RNTCP. 176 (68%) preferred chest x-ray to sputum examination for TB diagnosis. Only 70 (27%) prescribed alternate day regimen. Majority (75%) expressed no faith in RNTCP while 89% opined that maintenance of prescribed RNTCP documents was too difficult. About two-third uninvolved PPs were willing to get involved in RNTCP. Majority (98%) of PPs recommended appreciation by government as a way for increasing their involvement.

Conclusion: Knowledge and involvement of PPs in RNTCP in Hooghly district were low. Regular training, greater interaction with programme officers and adequate incentives in different public-private partnership schemes could increase the involvement of PPs in RNTCP as well as increase their knowledge about diagnosis and management of TB patients. **[*Indian J Tuberc 2010; 57:* 199-206]**

Key words: Tuberculosis, RNTCP, India, Practitioners

INTRODUCTION

India accounts for one fifth of global incidence of tuberculosis (TB), two-thirds of total cases in South-East Asia and tops the list of the 22 high burden countries in the world.[1] TB is a major cause of mortality in India with more than 2,76,000 deaths every year.[1] The Indian Revised National Tuberculosis Control Programme (RNTCP) began large-scale nationwide implementation of the World Health Organization's global TB control strategy in 1998 and by 2006, the DOTS programme was implemented in all the 633 districts of the country.[2]

In India, private practitioners (PPs) of medicine are widely distributed both in rural and urban areas.[3] The private sector accounts for 82% of all out-patient visits at all India level, with no significant variations by income group.[3] PPs in India treat over half of the TB patients. These are often not notified to the public health system and therefore not recorded in official statistics.[4] For the RNTCP to broaden its reach and have maximal impact, the involvement of private practitioners in the programme assumes great importance. Several studies in India and elsewhere have convincingly shown that involvement of PPs in RNTCP is associated with improved case notification and good treatment outcomes.[5,6] However, in many parts of India, the private sector has still remained alienated from DOTS implementation. As a result, case detection has remained low in many of these regions. Studies have also shown a gross lack of knowledge of PPs about diagnosis and treatment of TB. Case management practices in the private sector overly rely on X-ray for diagnosis as well as monitoring of

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TB treatment, and the use of sputum microscopy is low, ranging between 12 and 50%.[3] Treatment of TB patients is often based on unproven and untested regimens.[4]

In Hooghly district of Indian state of West Bengal, RNTCP was started as a pilot project in 1995 covering a population of 0.45 million. In spite of the adequate infrastructure and programme being in place for more than 13 years, the district is still lagging behind in achieving the minimum expected case detection of 70%. During the fourth quarter of 2006, the new sputum smear positive and the total case detection rates in the district were 47/100,000 and 117/100,000 respectively as against the target of 53/100,000 and 142/100,000 population. These rates were also lower than the state figures of 65/100,000 and 137/100,000 population.[5] Public-Private Mix (PPM) project is still in its initial phase in the district and poor involvement of PPs could be one of the important reasons for low case detection.

We conducted a cross-sectional study among PPs in Hooghly district to assess their knowledge, attitudes and practices about diagnosis and management of TB and RNTCP. We also assessed the involvement of PPs in RNTCP including the reasons for non-involvement.

METHODS

Study population: We conducted a cross-sectional study covering all the 695 private allopathic physicians practising in Hooghly district registered with the district branch of Indian Medical Association (IMA) during May and December 2008. Allopathic private practitioners working in the government hospitals were excluded. We also excluded the practitioners of other systems of Indian medicine as only the physicians with minimum MBBS qualification are eligible to provide diagnosis and treatment of TB patients under RNTCP.[6]

Sample size and sampling procedure: Assuming 50% of PPs had adequate knowledge, confidence interval of ± 5%, confidence co-efficient of 95%, and non-response of 5%, we calculated the sample size as 260. We randomly selected 260 PPs from the IMA list of registered allopathic physicians in the district.

Data collection: With the help of District TB officer (DTO), consultant of German Leprosy and TB Relief Association and district IMA officials, we organized three Continuing Medical Education (CME) programmes at Chinsurah, the district headquarter and Arambagh and Serampur sub-divisions. We invited the randomly sampled PPs to attend these CME programmes. PPs, who could not attend the CMEs, were contacted in their clinics. We used a self-administered, pre-tested, structured questionnaire to collect the data. The questionnaire had two parts: the first part covered information regarding training received under RNTCP, investigations prescribed for diagnosis of TB, treatment regimens used including provision of treatment under supervision and health education given to the TB patients. The second part sought information about their involvement in RNTCP, reasons for non-involvement and recommendations for involving the PPs in the programme.

We considered a PP as involved in RNTCP if he/she was officially registered in any of the five schemes of the programme. [5]

Human subject protection: The institutional ethics committee of National Institute of Epidemiology, Chennai approved the study protocol. We obtained written informed consent from all the PPs before administering the questionnaire.

Data analysis: We used Epi-Info software (version 3.3.2) to calculate the proportions of different variables and compared them using chi-square test.

RESULTS

Out of the 260 PPs interviewed, 174 (67%) attended the CME while the rest were contacted in their clinics.

General characteristics: Of the 260 PPs interviewed, 184 (71%) were males, 194 (75%) were in the age group of 30-50 years, 134 (51%) were practising for less than five years and 136

(52%) had post-graduate medical qualifications. Two hundred forty two (93%) were seeing TB patients on a regular basis (Table-1).

Knowledge about DOTS: Fifty-seven (22%) PPs had attended modular training on RNTCP while 198 (76%) PPs were sensitized in various other workshops. Seventy (27%) PPs were of the opinion that DOTS was based on scientific evidence and were adequate for treating pulmonary and extra-pulmonary TB patients (Table-2).

Practices regarding management of TB patients: One hundred seventy six (68%) PPs preferred chest x-ray, while 45 (17%) preferred sputum examination as investigations for diagnosis of pulmonary TB in a suspected patient. Forty-nine (19%) PPs believed that sputum test was more reliable than chest x-ray. Only 45 (17%) PPs referred TB suspects to government hospital for diagnosis. One hundred and ninety (73%) PPs preferred daily regimens for treating their TB patients. All were using different combinations of two or more of the four first-line drugs, namely isoniazid (INH), rifampicin, ethambutol and pyrazinamide. Only 55 (21%) were using a four-drug regimen. Seventy (27%) PPs believed that anti-tuberculosis drugs could be given intermittently and that such regimen was better than

Table-1: General characteristics of the private practitioners (n=260) in Hooghly district, West Bengal, India, 2008

General characteristics	n	%
Age		
<30 yrs	11	4
30-50 yrs	194	75
>50 yrs	55	21
Sex		
Male	184	71
Female	76	29
Practising experience (years)		
<5	134	51
5-10	66	26
>10	60	23
Educational qualifications		
MBBS	124	48
MBBS with post-graduate diploma	58	22
MBBS with post-graduate degree	76	29
MBBS with super-specialization	2	1

Table 2: Knowledge, attitude and practices of private practitioners (n=260) about TB and RNTCP, Hooghly, West Bengal, India, 2008

Knowledge, attitude and practices	#	%
Training and sensitization about DOTS		
Underwent modular training in RNTCP	57	21
Attended RNTCP sensitization workshops	198	76
Academic knowledge by literature or journal review	167	64
Knowledge about DOTS		
DOTS is based on scientific evidence	70	27
DOTS regimen is adequate for pulmonary and extra-pulmonary TB	70	27
DOTS is cost-effective, has less side effects and easy to administer	70	27
Alternate day regimen has same efficacy as daily regimen	70	27
Three samples of initial sputum test necessary	68	26
Attitudes about DOTS		
PPs were officially registered in the scheme-1 of RNTCP	29	11
Timing of DOTS is not convenient for TB patient	224	86
Treating TB patients is more popular in private sector	242	93
Quality of TB medicine supplied in the programme is not good	104	40
Preferred investigation for diagnosis of TB		
Chest x-ray alone	176	68
Sputum examination	45	17
Both sputum test and chest x-ray	23	9
No preference	16	6
Referred TB cases to Govt. sector	45	17
Sputum test is more reliable for diagnosis	49	19
Treatment of TB patients		
Treats TB patients regularly	242	93
Prescribe daily regimen	190	73

Table-3: Knowledge of PPs about TB and RNTCP according to involvement in Scheme 1 of RNTCP. Hooghly, West Bengal, India, 2008

Characteristics	Frequency: Among involved (n=29) #	%	Among uninvolved (n=231) #	%	χ^2	p
Trained in RNTCP	5	17	52	23	0.17	0.68
Sensitized in RNTCP	29	100	169	76	8.80	<0.00
Knowledge of DOTS	10	35	58	25	0.74	0.39
Attended CME programmes organized by IMA	5	17	40	19	0.06	0.8
Three sputum samples necessary for diagnosis	10	35	58	25	0.73	0.39
Preferred chest x-ray for diagnosis	24	83	152	66	2.66	0.10
Prescribing daily regimen	25	86	165	71	2.16	0.14
Monitoring of patients on treatment by chest X-ray	5	17	231	100		<0.00*

(*Fisher exact test)

Table-4: Reasons for non-involvement of private practitioners in RNTCP (n=231), Hooghly, West Bengal, India, 2008

Reasons for non- involvement	#	%
Will lose non-TB patients if officially involved in RNTCP	212	92
No supervision by Govt. machineries is acceptable	210	91
Maintaining documents of TB patients is a problem	205	89
No one approached for involvement	192	83
PPs will have to be answerable to the Govt health system	182	79
Workload will be more if get involved in RNTCP	182	79
No faith on the government health system	172	75
De-motivation because no. of patients will come down if get involved in RNTCP	121	52
Will lose money if officially in RNTCP	45	20
Health staff do not visit	29	13
Incentives in different schemes is inadequate	25	11

Table-5: Suggestions of uninvolved private practitioners (n=231) for their better participation and future involvement in RNTCP, Hooghly, West Bengal, India, 2008

Suggested recommendations	#	%
Recognition or appreciation by the Govt. sector	227	98
IMA-Govt. collaboration is necessary for better pursuance	227	98
Frequent contact with DTO and key persons of RNTCP to increase mutual trust	227	98
Exclusive staff for PPM project for better implementation	200	87
Timely and automatic payment to private practitioners in different schemes	30	13
Regular CME by IMA	28	12
Willing to get involved in RNTCP in future	144	62

daily regimen, considering its cost, side effects and ease of administration. Majority of the PPs (91%) informed that they would advise chest x-ray while the rest preferred sputum test for monitoring the treatment of TB patients. PPs advised TB patients about covering the mouth while coughing and maintaining good hygiene (38%), taking the treatment regularly (17%), not smoking during treatment (17%), good diet (21%) and safe disposal of sputum (12%). Only 34(13%) PPs advised sputum positive patients to take special care of children below six years who come in their contact and to take INH chemoprophylaxis (Table-2).

Involvement in RNTCP: Only 29 (11%) PPs were officially registered in the scheme-1 of RNTCP. As per the scheme-1, PPs referred TB suspects to public health facilities for diagnosis. Significantly higher proportion of involved PPs was sensitized about the programme. As compared to involved PPs, un-involved PPs more commonly used chest x-ray for monitoring their TB patients on treatment. (Table-3).

Reasons for non- involvement in RNTCP: The common reasons cited by 231 PPs for their non-involvement in RNTCP included unacceptability of supervision by government machineries (91%), difficulty in maintaining documents of TB patients (89%), increase in workload if involved in RNTCP (79%) and no faith on government health system (75%). Un-involved PPs also felt that they would lose non-TB patients attending their clinics (92%) or money (20%) while 40% felt that the quality of TB drugs given under the programme was not good. Majority (83%) informed that nobody from the programme approached them to get involved (Table-4).

Measures suggested for increasing the involvement of PPs: One hundred forty four (62%) un-involved PPs were willing to participate in RNTCP. Un-involved PPs were of the opinion that involvement could be increased by regular interaction with DTO and key programme functionaries (98%), recognition or appreciation by government (98%) and provision of exclusive staff for PPM project (87%). Only 13% mentioned about timely payment to involved PPs under different RNTCP schemes (Table-5).

DISCUSSION

Involvement of PPs in TB control programme plays a crucial role in increasing case detection and improving treatment outcomes. As large proportion of TB patients in India is first seen and treated by PPs, TB control programme in a given

area cannot reach its goals without the participation of the private sector.[2,4] The findings of our study indicate that in Hooghly district, the involvement of private sector was minimal. Their knowledge about RNTCP and management of TB as per guidelines was inadequate. Only one fourth of PPs attended a modular training programme in RNTCP.

RNTCP recommends examination of three (recently two) sputum samples for diagnosis of TB. Patients on treatment need to be monitored by sputum examination at the end of intensive and continuation phase of the treatment. In Hooghly, chest X-ray was the preferred diagnostic tool for two thirds of PPs while only one fourth appreciated the importance of three sputum examinations. Even for monitoring of TB patients on treatment, most of the PPs preferred X-rays. Except for a study conducted in New Delhi, most of the studies conducted in India reported the over-reliance of PPs on x-rays.[5,8,9] The excessive use of x-rays in Hooghly district could either be due to lack of awareness among the practitioners about the reliability of sputum examination for diagnosis of TB. Supervised, intermittent treatment is a well-established strategy for the treatment of TB under RNTCP. Majority of the PPs in Hooghly district prescribed daily regimen and used different combinations of the four first-line drugs. Similar findings were reported by various studies conducted in India.[3,5] A study in Maharashtra, India reported that many PPs prescribed inappropriate TB drugs and did not provide supervised treatment.[10] It also showed that PPs prescribed different regimens, most of which were both inappropriate and expensive.[10] A study conducted in Delhi found that only 29% of the PPs were using the regimen recommended by the RNTCP and only 8% knew the correct dosage combination of anti-tubercular treatment.[3]

Very small proportion of PPs in Hooghly was involved in RNTCP. However, the knowledge about investigation of suspected patients as well as treatment regimen was not different among involved and un-involved PPs. This could possibly be due to two reasons. Firstly, all the involved practitioners were registered in scheme-1 of RNTCP in which PPs refer suspected TB patients to designated microscopy centres for diagnosis. Secondly, only a small proportion of involved PPs were trained in RNTCP, although, as per RNTCP guidelines, PPs have to undergo a two-day modular training after getting involved. It is thus necessary to make organized efforts to increase the awareness of PPs about RNTCP.

Although not systematically examined in this paper, we hypothesize that the low new sputum positive and annualized case-detection rates in the district could be on account of the low involvement of PPs. The commonest reasons cited by PPs for their non-involvement was related to their poor faith in the government health system and their apprehension that the work load would increase. Many PPs also felt that non-TB patients would not attend their clinics if they come to know that TB patients are being treated in their clinics. Involving PPs in the programme is a challenge in the district and programme managers need to make a sustained effort towards engaging them. They need to build a mutual trust with the PPs, educate them about different schemes of programme and clarify their doubts in order to increase their participation in the programme. Several PPs suggested that such a trust could be built by frequent contact by DTO and other key programme functionaries. A large proportion of PPs in the district wanted to be a part of RNTCP. This willingness could be utilized for building public private partnership for control of tuberculosis in Hooghly. Their involvement in the programme would also increase their awareness about recommended investigations for diagnosis of cases and their appropriate management.

The main limitation of our study was that we used self-administered questionnaire to collect data regarding knowledge, attitude and practices of PPs and their involvement in RNTCP. Though we could not validate their responses about their knowledge, attitude and practices in RNTCP, information about their involvement was cross-checked with the RNTCP records.

In conclusion, the involvement of PPs in RNTCP in Hooghly district is low. Their knowledge about use of sputum microscopy for

diagnosis of TB, treatment monitoring as well as treatment regimen is inadequate. It thus becomes imperative to not only increase the awareness about RNTCP among the PPs but also actively engage them in the programme in order to have maximal impact on TB control in the district. Organized efforts are needed to increase the awareness of PPs about RNTCP. Further, the DTOs need to maintain regular contact with the PPs, so as to explain about different schemes of the programme and remove the apprehension that their participation in RNTCP will increase their workload.

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Original Article

UTILITY OF MICROSCOPIC OBSERVATION OF DRUG SUSCEPTIBILITY (MODS) ASSAY FOR *MYCOBACTERIUM TUBERCULOSIS* IN RESOURCE CONSTRAINED SETTINGS

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Summary

Introduction: Multidrug Resistant Tuberculosis (MDR TB) is a global health problem. Conventional techniques or automated systems for diagnosis and drug susceptibility testing are either comparatively slow or costly. Microscopic Observation Drug Susceptibility [MODS] assay is a simultaneous detection and direct drug susceptibility test [DST] method which relies on the characteristic growth of *Mycobacterium tuberculosis* (MTB) in a liquid medium.

Aim: Comparison between MODS assay and culture on Lowenstein Jensen (LJ) medium with respect to;

i) detection of mycobacterial growth and time taken for culture positivity

(ii) to compare concordance of susceptibility results of MTB isolate by MODS with proportion method using LJ medium.

***Method*:** A prospective study was carried out on 171 acid fast smear positive sputum specimens. The decontaminated sediment was used for culture and DST using LJ medium (proportion method) and MODS assay plates containing supplemented Middlebrook 7H9 broth with and without critical concentrations of isoniazid and rifampicin.

***Results*:** Median time to growth and DST using MODS assay was 10 days and that with LJ medium was 24 and 66 days respectively. The sensitivity and specificity of MODS assay was 100%. All the isolates were characterized as MTB. MODS demonstrated 98.8% and 99.4% concordance for isoniazid and rifampicin respectively and 100% for MDRTB. Positive and negative predictive value for MDRTB was 100%.

***Conclusion*:** MODS assay offers a rapid, simple, economical and feasible method for simultaneous culture and DST of MTB. Utility of MODS needs to be ascertained in extrapulmonary TB cases.

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Key words: *M.tuberculosis,* Multidrug resistance, Drug susceptability test.

INTRODUCTION

India bears the brunt of 1/5th of the global tuberculosis [TB] burden. In 2008, the annual incidence was 1.9 million cases, of which 0.8 million were infectious new smear positive pulmonary TB [PTB] cases[1]. Prevalence of MDRTB in new cases and previously treated cases is reported as 3% and 12-17% respectively[1]. The global emergence of Extensively Drug Resistant Tuberculosis [XDRTB] has only complicated the problem.

Under the Revised National Tuberculosis Control Programme [RNTCP], sputum microscopy forms the mainstay for diagnosis as well as for monitoring response to therapy. But it cannot be used for assessing drug susceptibility status[2,3]. Under RNTCP, treatment failure is predicted based on continued or new smear positivity at the end of fifth month of Antituberculosis Treatment (ATT). Such patients are then advised culture and drug susceptibility testing [DST], the time lapse that compromises on success of therapy and results in spread of MDRTB for longer periods[4].

There is an urgent need to identify methods that would rapidly detect both the presence of *Mycobacterium tuberculosis* [MTB] and drug resistant status. Culture based methods are considered as the gold standard[4]. However, these

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methods require moderate to prolonged incubation time or expensive equipment and reagents. Molecular tools perform robustly for both detection and drug resistant status determinations, but are costly, a feature not many laboratories can afford. Improvisations using liquid culture media which do not require expensive equipment and consumables have been reported to perform well. Most of these are indirect DST, with MTB isolation on solid media being a prerequisite[5-8].

Ours is a tertiary care teaching hospital where on an average 10,000 patients are screened annually for TB, free of cost. It was therefore important to identify tests that would be economical, yet reliable. The Microscopic-Observation Drug-Susceptibility (MODS) assay is a novel, rapid, simple, tissue culture based direct assay which relies on formation of characteristic cord like growth of MTB in liquid culture medium[9].

The present study was undertaken in smear positive patients to compare MODS assay and culture on Lowenstein Jensen (LJ) medium with respect to sensitivity of detection of mycobacterial growth and time taken for culture positivity. Also to compare concordance of susceptibility results of MTB isolate by MODS with proportion method using LJ medium.

MATERIAL AND METHODS

After obtaining Institutional Ethical Committee's permission, a prospective study was undertaken over a six month period, on newly diagnosed sputum smear positive PTB patients. Patients receiving ATT were excluded. The work was carried out in Class II Biosafety Cabinet and level two biosafety practices were followed. Dedicated reagents for decontamination of each specimen and strict aseptic practices were followed to prevent cross contamination[10]. The identity of the isolate was blinded for the two methods [MODS and LJ].

I) **Microscopy**: All sputum samples were processed for acid fast microscopy and reported according to RNTCP guidelines[2].

II) **Decontamination and concentration**: Smear positive samples were digested and decontaminated using NALC-NaOH method as per standard protocol and then centrifuged at 3000g for 15 minutes[4]. The sediment was used for further processing. All reagents for media preparation and antibiotic powders were obtained from Himedia.

III) **MODS assay:** The procedure was carried out as described by Moore *et al*[9].

A) **S**upplemented Middlebrook (MB) 7H9 broth and working concentration of INH (4µg /ml) and RIF (10µg /ml) were prepared.

B) **Inoculation of MODS plate**: 500µl of decontaminated sediment was suspended in 4.8 ml of supplemented MB 7H9 broth (sample-broth mixture). This was used to inoculate 24 wells sterile tissue culture plates [Becton and Dickinson, USA] for MODS assay. For each sample, four wells in a column of a tissue culture plate were used (two drug free controls and two drug containing wells). To each of the four wells, 900µl of sample-broth mixture was added keeping 1.7 ml of sample-broth mixture as "backup". In the first two wells, 100µl of supplemented MB 7H9 broth was added. These two wells acted as growth controls. In the third well, 100µl of INH (4µg/ml) was added to obtain the final concentration of 0.4µg/ml. In the fourth well, 100µl of RIF (10 µg/ml) was added to obtain the final concentration of 1µg/ml. In each plate, column three was used as negative control containing only supplemented MB 7H9 and either INH or RIF. Any growth in this lane indicated cross contamination. On each processing day, two positive controls were run. H37RV was used as a drug sensitive control and one known MDR strain was used as drug resistant control. Tissue culture plates were sealed in plastic zip lock bags and were incubated at 37°C.

D) **Reading of MODS Plates**: The plates were examined daily within the zip lock bags only, using an inverted microscope beginning from day three. MTB growth was reported qualitatively by visualization of the characteristic serpentine or tangled cord like growth formation. The reading for

DST was taken on the same day as culture positivity in control well. Bacterial or fungal contamination was identified by clouding of media within three days of inoculation. "Backup" samples were decontaminated and recultured with minimal delay. A negative MODS culture was discarded after 21 days.

E) **Interpretation and performance of MODS assay:** Growth in control wells, without growth in drug containing wells was recorded as sensitive. If growth was detected in both control and drug containing well, it was reported as resistant. Sensitivity and specificity were calculated by constructing the two by two table of paired data with results of the LJ method taken as the gold standard. Kappa statistics was used to test agreement between DST results of MODS and LJ method.

IV - A) **Culture on LJ medium:** Decontaminated sediment was inoculated on LJ medium. Reading of culture and speciation of isolates as MTB or MOTT was done as per WHO protocol[4].

B) **DST by proportion method:** DST by proportion method was as described by Canetti *et al*[11]. The standard strain H37RV was obtained from the Mycobacterial repository at the Central JALMA Research Institute, Agra. LJ medium was prepared and tested for quality control as per WHO guidelines[4]. An in-house clinical isolate previously characterized as MDR was used as drug resistant control.

The turnaround time was the time taken from the date of inoculation to the date on which confirmed growth was visualized. The result of the MODS assay was considered concordant if it was similar to the result obtained by using the conventional LJ method, for both culture and DST.

RESULTS

171 sputum smear positive specimens obtained from an equal number of pulmonary tuberculosis patients were processed. 11 specimens were found contaminated (both LJ and MODS in five, only LJ in one and only MODS in five). Further analysis of the remaining 160 specimens is presented here. All 160 isolates were characterized as MTB and all demonstrated cord formation in the MODS assay.

Turnaround time for culture positivity

The median turnaround time for culture positivity using LJ medium and MODS assay was found to be 24 days (range 20-28 days) and 10 days (range 9-14 days) respectively.

Turnaround time for DST

Culture and DST being concurrent in MODS assay, the median turnaround time for DST was the same as that for culture. The median turnaround time for DST using LJ medium was 66 days. 89.4% of the DST results using MODS assay were obtained by the 12th day and all 100% by 14th day.

Susceptibility pattern by proportion method

The proportion of strains demonstrating sensitivity to both INH and RIF were 54.4%. Monoresistance to INH and RIF was observed in 15.6% and 10% of strains respectively. 20% of the strains were MDR TB.

Agreement between MODS assay and proportion method for DST (Table)

Of the 160 isolates tested, complete agreement on DST results were obtained in 157 (98.1%). Of the discordant results, two strains classified as susceptible to INH and one strain classified as susceptible to RIF by proportion method were detected as resistant by MODS assay. No discrepancy was observed with the MDR strains. The agreement on INH DST and RIF DST was 98.8% and 99.4% respectively. The sensitivity and specificity for INH and RIF DST was found to be 100%, 98.1% and 100%, 99.1% respectively.

Table: Comparison of DST results by MODS assay and proportion method

INH and RIF	Proportion method	MODS assay
Both sensitive	87	84
Both resistant (MDR)	32	32
Only INH resistant	25	27
Only RIF resistant	16	17
Total	160	160

DISCUSSION

Early detection of drug resistance is the key point in effective control of drug resistant TB. Culture and DST using conventional methods are time-consuming while automated methods tend to be expensive, limiting their use in resource constrained settings[12,13]. Hence there is need for a rapid, reliable and cost effective test for detection of drug resistance. MODS assay has the advantage of simultaneous detection and DST of MTB.

In the present study on new smear positive patients, the culture positivity rate was 100% (excluding contamination) for both MODS assay as well as LJ medium. Very high culture positivity rates (92%-98%) using MODS assay have been observed in studies which have included even smear negative patients[14-16]. The high culture positivity rate in the present study is due to the inclusion of only known smear positive patients.

All 160 isolates were identified as MTB. The prevalence of MOTT in studies from India varies from 1.4% to 8.8%[10,17-19] and is a reflection of its environmental predominance and the patient population.

In the present study, MODS took a median time of 10 days to culture positivity as compared to 24 days using LJ medium and this difference was statistically significant (p value- 0.014). In other studies, the turnaround time has ranged from seven to nine days in smear positive patients and six to 10 days in smear negative patients[10,14-16,20-22].

A number of new simple and inexpensive methods for DST have been recently described. Most are indirect tests requiring pure *M. tuberculosis* isolates which take at least three weeks and involve the potential laboratory biohazard of culture manipulation[5-7]. A study reported from this institute based on ability of MTB to reduce nitrate to nitrite was found to be useful[8]. However, MODS has the greatest advantage that it is a direct assay. In the present study, the median time for DST results by MODS and by proportion method was 10 and 66 days respectively. This difference was found to be statistically significant (p value - 0.01). Mengatto *et al* observed that the average time required to obtain DST result by MGIT and MODS was comparable[23].

Complete agreement on DST results by MODS and proportion method was obtained in 98.12% of cases. Both methods detected 20% isolates as MDRTB and there was no discrepancy between the two methods. A study undertaken for the first time in RNTCP outpatients in Mumbai in the year 2009 revealed a high proportion of MDRTB in both previously untreated (24%) and treatment-failure cases (41%)[24]. Being a tertiary care centre, the proportion of MDRTB cases may be high as compared to the national average.

Sensitivity and specificity of MODS for detection of INH and RIF resistance was very high and so was the agreement for INH and RIF DST. No major discrepancy was detected. Any discrepant results were observed with three isolates. MODS reported three isolates as resistant which were sensitive by proportion method. MODS assay is a qualitative test as against the conventional DST methods which are semi-quantitative. Hence, MODS can tend to report an isolate as resistant which is reported as sensitive by proportion method. Another possible explanation for discrepant results could be slightly different bacterial inoculum size due to sampling error. The results of the present study are as reported in literature and encouraging[14,20,25].

Cost of detection and DST (for INH and RIF) by MODS , including the cost of tissue culture plate, reagents and drugs without the cost of infrastructure, equipment and manpower , was Rs 80/- . It is cheaper than DST using LJ medium (Rs 700/-) and automated gold standard methods like MGIT (Rs 2200/-).

Enhanced sensitivity of MODS assay would likely be beneficial from both public and individual health standpoints[16]. In addition, unlike smear microscopy, the MODS assay can also be used for speciation and direct DST.

MODS assay has several other advantages. If the MODS culture is negative at three weeks, it is considered true negative as against six weeks by proportion method[9]. By using low critical concentration of RIF (1µg/ml), MODS can be used as a screening test for early isolation of infectious patients who have a high likelihood of MDR TB infection[21]. As all XDRTB cases are by definition MDRTB cases, MODS assay is a potentially useful tool for screening population to detect XDRTB isolates. The technique does not require manipulation of positive cultures as MODS plate is permanently sealed after inoculation, thus minimizing potential biohazard.

Some limitations of the test need to be highlighted. The initial standardization to get conversant with characteristic cording using standard strains and known clinical isolates was important and took more than a month. J.S. Michael *et al* have reported that more extensive training and standardization is required before conducting any study using MODS assay[26]. The present study showed a contamination rate of 5.26% (9/171) with MODS assay, and 4.09% (7/171) with LJ medium. The contamination rate in the present study is similar to that reported in literature[15,25]. The MODS methodology inherently protects against cross-contamination from the point of sample inoculation onward because the culture is then sealed within a transparent plastic bag. Sufficient care was taken while processing the specimen to avoid cross contamination[10]. Maximum contamination was observed in the initial phase of the study and then the practice of dedicated decontamination and asepsis was strengthened and continuously monitored. These two aspects along with stringent biosafety practices need to be given due attention for the assay to work successfully. Results of identification of MTB by MODS are presumptive as *M. chelonae, M. smegmatis and M. bovis* also form cord like growth. Also, for obtaining faster results, daily microscopic reading is required.

Once standardized, MODS assay is feasible to perform in resource constrained settings with trained manpower. The equipment required for MODS assay is similar to that required for culture of mycobacteria. Inverted light microscope is the only item which many laboratories lack and need to invest in.

Based on the results of the present study and available literature, it can be stated that MODS assay can be used for early and accurate detection of MTB and MDRTB. Given its simplicity, low cost and reduced turnaround time (within two weeks), it would be an excellent method for routine tuberculosis testing in developing countries. Utility of MODS needs to be ascertained in extrapulmonary TB cases.

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Case Report

MYCOBACTERIUM TUBERCULOSIS CAUSING INFECTION OF AN IMPLANTABLE BIVENTRICULAR DEFIBRILLATOR

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Summary: Mycobacterial infection of implantable cardiac devices is rare, and infection of pacing system components with *M. tuberculosis* has been reported on only three previous occasions, involving epicardial pacing systems in two cases. We report here a pocket infection with *M. tuberculosis* in a transvenous biventricular defibrillator. **[*Indian J Tuberc 2010; 57:* 213-215]**

Key words: *M. tuberculosis*, Pacemaker, Defibrillator

INTRODUCTION

Infection of implantable cardiac devices by mycobacterium species, particularly *M. tuberculosis*, is rare. Mycobacterial infections may present many years after a procedure, often in a non-specific fashion and without visible sign of infection. Two reported cases of tuberculous infection involved epicardial pacing wires, suggesting perhaps that placement of epicardial wires may be associated with reactivation of previously silent pericardial infection. We hypothesise that our patient carried mycobacterial infection which seeded onto the device pocket at the time of his revision procedure, and subsequently remained clinically silent in the vicinity of the device for several months. Florid evidence of pocket infection with a fully sensitive organism was eventually present despite almost six months of anti-tuberculous therapy, probably due to poor penetration of anti-tuberculous drugs into the device pocket. The relatively low CRP at the time of presentation suggests that the tuberculous infection was confined to the device pocket, without provoking a significant systemic inflammatory response.

CASE REPORT

A 67-year-old man underwent implantation of a biventricular implantable defibrillator (ICD) due to heart failure and severe left ventricular systolic dysfunction. Two years later the device was revised due to a failed left ventricular lead. The redundant lead was easily extracted, however due to bilateral occlusion of the subclavian veins, it proved impossible to place a new lead.

A few months later, the patient presented with fatigue, weight loss and anaemia. It was noted that the patient had moved away from the Indian subcontinent to the United Kingdom at 19 years of age, and there was no family history or known recent contact with tuberculosis. Computed tomography imaging demonstrated extensive thoracic and abdominal lymphadenopathy, felt to be consistent with disseminated tuberculosis. The patient was not considered suitable for surgical lymph node biopsy, and broncho-alveolar lavage failed to produce any diagnostic microbiological information. Human

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Table: Mycobacterial Infections of Implanted Pacemakers as reported in literature.

Year	Age	Procedure	Organism	Outcome
1996[1]	70	Transvenous pacemaker	*M. tuberculosis*	Patient died of military tuberculosis
1998[4]	68	Epicardial pacemaker	*M. abscessus*	Device extracted, patient died
1998[5]	74	Pacemaker	*M. chelonae, M fortuitum*	Device extracted, successful eradication
2004[6]	53	Transvenous ICD	*M. abscessus*	Device extracted, successful eradication
2005[7]	62	Transvenous pacemaker	*M. fortuitum*	Device extraction, successful eradication
2005[2]	8	Epicardial pacemaker, congenital heart surgery	*M. tuberculosis*	Device extraction, successful eradication
2006[8]	80	Pacemaker	*M. fortuitum*	Device left in-situ, successful eradication with antimicrobial therapy
2007[8]	84	Revision of transvenous pacemaker	*M fortuitum*	Device extraction, successful eradication
2009[3]	80	CABG surgery and epicardial pacing wires	*M. tuberculosis*	Drainage of abscess cavity

Immunodeficiency Virus (HIV) testing was not performed. Empirical anti-tuberculous therapy was commenced.

Almost six months later, the patient presented with pain around the ICD site, associated with a fluctuant swelling. No fever was present, and inflammatory markers were mildly elevated (C-reactive protein 17 mg/L). Ultrasound confirmed a 6x5cm collection adjacent to the ICD from which pus was aspirated. Microscopy and culture confirmed the presence of *M. tuberculosis* bacilli, fully sensitive to standard anti-tuberculous chemotherapy.

The ICD was explanted, and the patient discharged with a Lifevest; a wearable external defibrillator which allows treatment of life-threatening arrhythmias pending eradication of the infection and future re-implantation. Unfortunately, despite the use of the Lifevest, the patient died of malignant ventricular arrhythmias whilst undergoing anti-tuberculous therapy.

DISCUSSION

Three reports of tuberculous pacing system infections exist in the literature. The first is an elderly patient who had undergone single chamber pacemaker implant 20 years previously, and presented with miliary tuberculosis involving the heart and pacemaker pocket[1]. The second is a child with congenital heart disease who had an implant of an epicardial pacemaker[2]. Several months later, the patient presented with general ill-health and mild fever associated with a lump at the pacemaker site. Surgical drainage and extraction of the pacemaker

demonstrated acid-fast bacilli at microscopy, and Polymerase Chain Reaction (PCR) confirmed *M. tuberculosis*. The third case also occurred at the site of epicardial pacing wires, which had been placed 11 months previously during coronary artery bypass surgery[3]. Drainage of the associated abscess confirmed *M. tuberculosis* infection.

Small numbers of cases of pacemaker infections associated with other mycobacterial species have also been reported including *Mycobacterium fortuitum*, *Mycobacterium abscessus*, *Mycobacterium chelonae* and *Mycobacterium avium complex*[4-8]. Reports of mycobacterial infections are summarised in Table.

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Case Report

INTESTINAL TUBERCULOSIS IN A CELIAC DISEASE PATIENT

Sumitoj Singh[1], Sudhir Khichy[2], Deepak Bhangale[3] and Satinder Pal Aggarwal[4]

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***Summary*:** Both intestinal tuberculosis and celiac disease can cause malnutrition and failure to thrive. High index of suspicion is required to diagnose intestinal tuberculosis in a known case of celiac disease as both conditions present with similar complaints. We report a case of celiac disease with intestinal tuberculosis and perforation peritonitis. **[*Indian J Tuberc 2010; 57:216-219*]**

Key words: Intestinal Tuberculosis, Celiac disease, Perforation peritonitis.

INTRODUCTION

Celiac disease (gluten sensitive enteropathy), is an autoimmune disorder that occurs in genetically susceptible individuals following ingestion of gluten, a protein found in wheat, rye, and barley. The disease has a wide spectrum of clinical manifestations from asymptomatic to symptomatic disease. The common symptoms include chronic diarrhoea (71%), postprandial bloating (44.4%), mild abdominal discomfort (27%), refractory anaemia (95%), short stature (31%), metabolic bone disease, and delayed puberty (11%). Celiac disease is associated with other systemic abnormality like diabetes mellitus, hypothyroidism, thalassemia, IgA nephropathy and cirrhosis[1].

India is the highest tuberculosis burden country globally, accounting for one fifth of the global incidence. Gastrointestinal tuberculosis is the sixth most frequent form of extra-pulmonary site[2]. It has also wide spectrum of clinical manifestations, including intestinal obstruction, perforation and malabsorption syndrome.

Celiac disease and intestinal tuberculosis account for 9 % and 4% respectively for malabsorption syndrome in northern India [3]. Tuberculosis accounts for 5-9 % of all small intestinal perforations in India[2]. Celiac disease complicating with enteropathy-type T- cell lymphoma can present with perforation peritonitis[4,5]. High index of suspicion is required to diagnose intestinal tuberculosis in a known case of celiac disease as both conditions present with similar complaints. We report a case of non-responding celiac disease with intestinal tuberculosis.

CLINICAL RECORD

A thirteen year female presented with chief complaints of pain abdomen, distension, and obstipation since three days. Patient was diagnosed with celiac disease two years' back for the complaint of failure to thrive. Upper gastrointestinal endoscopy showed mosaic pattern with nodularity and scalloping in duodenum, esophagus and stomach normal. Duodenal biopsy showed crypt hyperplastic subtotal villous atrophy with foveolar metaplasia. Tissue transglutaminase antibody IgA was 672U/ml (negative: <50U/ml) and Anti- endomysial IgA antibody was strongly positive. Patient was put on gluten free diet following which she started gaining weight and height. After nine months, tissue transglutaminase level was 24.9 U/ml and Anti- Endomysial IgA antibody was mildly positive.

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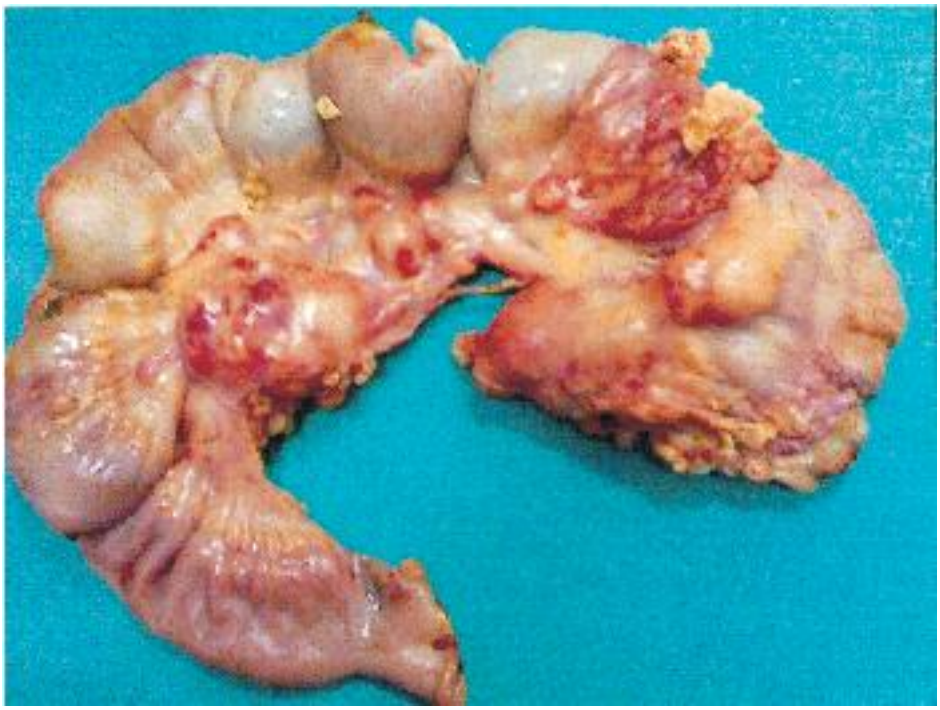

Figure 1: Terminal ileum with caecum and attached mesenteric mass.

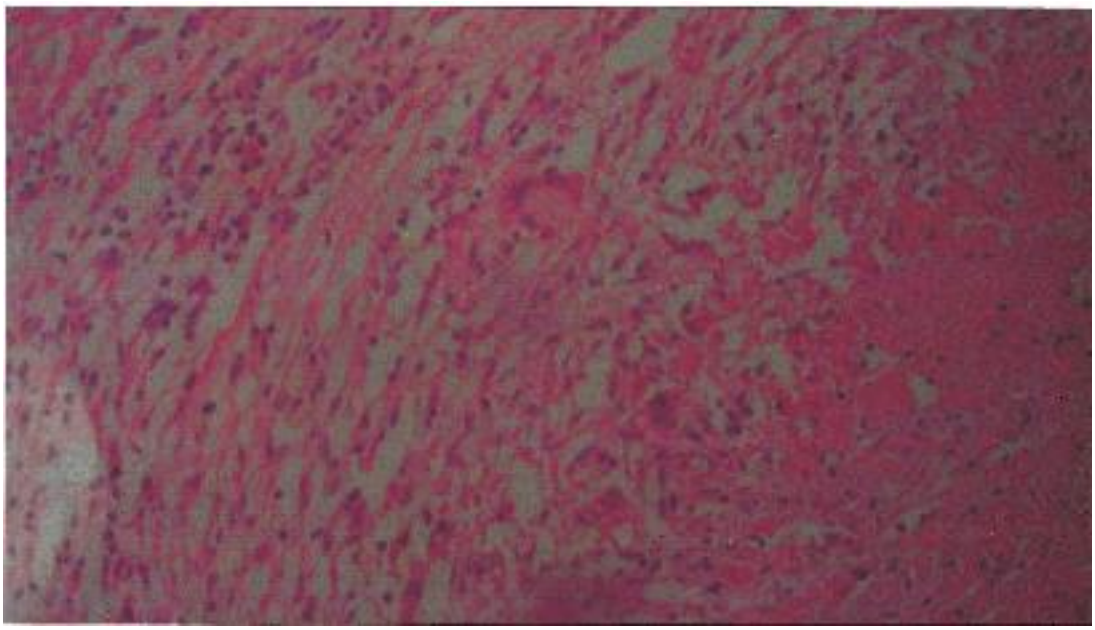

Figure 2: Caseating granulomas with Langhans' giant cells.

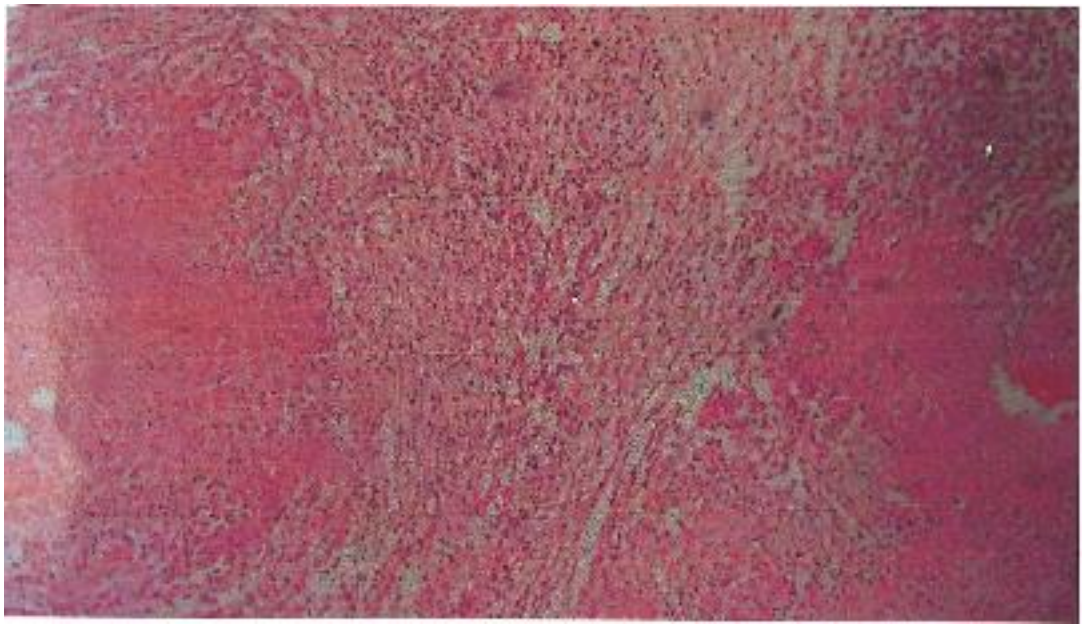

Figure 3: Caseous necrosis with lymphocytic cuffing.

Patient started complaining of pain abdomen for the last two months. Pain was in the epigastric region, mild in intensity, off and on and non-colicky in nature. There was no specific relieving or aggravating factor. It was associated with loss of appetite and weight. She lost about three kilograms in last two months. There was history of low grade fever off and on since two months. There was no associated history of chronic cough or recurrent subacute intestinal obstruction. Intensity of pain abdomen increased for the three days and it became generalized. It was associated with multiple, projectile, bilious vomiting and obstipation.

On examination, the patient was poorly built and nourished. She was four feet tall and weight was twenty kilograms. She had tachycardia (100/min), tachypnoea (20/min) and blood pressure was normal (110/70 mm Hg). Patient was anaemic and there was no lymphadenopathy. Chest auscultation revealed no abnormality. Abdomen was distended, generalized tenderness was present, and bowel sounds were absent.

Routine investigations were: Hb-8gm%, TLC- 9700/cu mm, DLC-N-78%, L-15%, M-02%, E-05%, Blood urea- 30mg%, Serum creatinine-1.0 mg%, Total serum protein- 7.6g% and Albumin-3.2g%. Chest Skiogram revealed air under diaphragm and no evidence of pulmonary tuberculosis. Patient was taken up for surgery after resuscitation. Intra operative findings were: there was one litre of bilio- purulent fluid in the peritoneal cavity, three perforations in the terminal ileum at anti mesentery border. Mesentery showed multiple enlarged lymph nodes, some matted to form nodal masses largest measuring 7.5 x 5 x 3.5 cm in the terminal ileum [Fig-1]. Resection of the perforation and lymph node bearing segment of the terminal ileum and caecum was done with end ileostomy and mucus fistula. On cut section, there were multiple ulcers in ileum and lymph nodes showed yellowish cheesy necrotic material. Biopsy was consistent with tuberculosis [Figs. 2 and 3] and there was no associated celiac disease at the particular site. Patient expired on seventh post operative day due to septicemia.

DISCUSSION

The link between celiac disease and tuberculosis was first reported by Williams H[6].

Williams A.J reported increased prevalence of past tuberculosis in adult celiac population. Of the seventy six adult celiac disease patients, six had history of tuberculosis and other seven patients had radiological evidence of tuberculosis. He postulated that the increased susceptibility to infection with tuberculosis in celiac disease is the result of depressed cell mediated immunity and/or malnutrition[7].

Ludvigsson *et al* investigated the risk of tuberculosis in 14,335 patients with celiac disease and found three - four fold increased risk of tuberculosis in celiac diseases[8]. They thought it to be due to deficiency of vitamin D and common genetic association of celiac disease and tuberculosis. Vitamin D deficiency in celiac disease occurs due to malabsorption and low content of Vitamin D in gluten free diet. Vitamin D activates the macrophages and induces the synthesis of nitric oxide in macrophages, which suppress the growth of Mycobacterium in these cells. Vitamin also promotes the differentiation of monocytes into epithelioid cells and multinucleated giant cells which form part of granulomas. A strong association exists between celiac disease and two human leukocyte antigens (HLA) haplotypes (DQ2 and DQ8). HLA-DQ2 haplotype is associated with specific alleles of HLA class I and class II molecules as well as with genes for TNF á and complement factors C2 and C4. Since C2 molecule is polymorphic and is important in mycobacterial invasion of macrophages, it is possible that particular C2 allele could promote tuberculosis infection in a subgroup of patients[8].

Non-responsive celiac disease occurs in seven to thirty per cent of the celiac disease patients. Unintentional gluten exposure is the most common cause (36%) and other etiologies include IBS (22%), refractory celiac disease (10%), lactose deficiency (8%), small intestinal bacterial growth (6%) and microscopic colitis (6%). The remaining 13% consisted of eating disorders, peptic ulcer disease, gastro paresis, crohn disease, food allergies, common variable immune deficiency and duodenal adenocarcinoma. Predominant symptoms in non-responsive patients included diarrhoea (54%), abdominal pain (55%), weight loss (20%) and fatigue (5%)[9]. Peter *et al* found a six fold increase in the risk of death from tuberculosis in patients with celiac disease[10].

Our patient was having increased abdominal pain and started losing weight since two months, while on strict gluten free diet, and was later on diagnosed as a case of intestinal tuberculosis. **Tuberculosis should always be included in the initial differential diagnosis of non-responsive celiac disease as incidence of tuberculosis is high in India and there is three-four fold increased risk of tuberculosis in celiac disease. High index of suspicion is required to investigate the patients for tuberculosis in celiac disease for early diagnosis and treatment to decrease the risk of death from tuberculosis.**

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Case Report

PRIMARY TUBERCULOSIS OF NOSE WITH INTRACRANIAL EXTENSION: A RARE PRESENTATION

Amit Pal Singh[1], Vikas Malhotra[2], Tripti Brar[3], A. K. Agarwal[4] and Nita Khurana[2*]

(Received on 11.8.2010; Accepted on 15.9.2010)

Summary: Tuberculosis continues to be a major public health problem. This disease has varying presenting features. We here present a case of primary tuberculosis of the nose with intracranial extension, a very rare presenting feature of tuberculosis. ***[Indian J Tuberc 2010; 57:220-222]***

Key words **:** Tuberculosis, Primary, Nose, Intracranial

INTRODUCTION

Tuberculosis (TB) is the world's leading cause of death from a single infective agent and a rising incidence has caused the World Health Organization to declare the disease a global emergency[1,2]. Despite the contact of pulmonary secretions and the mucous membranes of the upper respiratory tract with a high bacillary load, tuberculosis of the head and neck area, excluding laryngeal forms, is exceptional and constitutes only 2–6% of extra-pulmonary tuberculosis and 0.1–1% of all forms of tuberculosis[3,4]. Nasal tuberculosis (TB) comes mainly from the haematogenous or lymphatic extension of pulmonary TB; the nasal mucosa is not usually affected, despite being a point of entry for the *Mycobacterium tuberculosis*. Primary nasal TB (only affecting nasopharynx) is much rarer but can happen when the nasal mechanism of mucociliary clearance and lysosomal bactericidal activity fail[5,6]. We present a rare presentation of primary nasal tuberculosis with a intracranial extension in a young immunocompetent individual.

CASE REPORT

A four year-old boy came to our outpatient department with complaints of a low-grade fever of four months' duration and a bilateral nasal obstruction that had gradually increased in the last two months. There was gradual loss of vision in the last 15 days with no perception to light and to rays at the time of presentation. On physical examination, the boy was found to have mild right-sided proptosis and a visible expansion of the dorsum of the nose (Fig.1). Nasal endoscopy revealed the presence of a proliferative mass filling the right nasal cavity and the nasophyranx. No palpable neck nodes were detected, and systemic examination did not yield any significant findings. Contrast-enhanced computed tomography of the head and paranasal sinuses detected proliferative mass that filled most

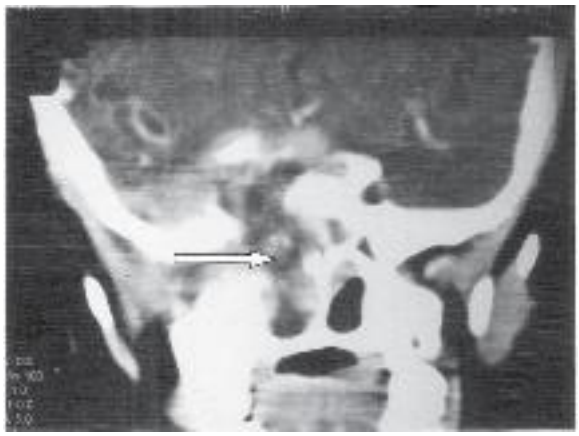

Fig. 1: CECT showing invasion of the mass in the orbit and intracranial region.

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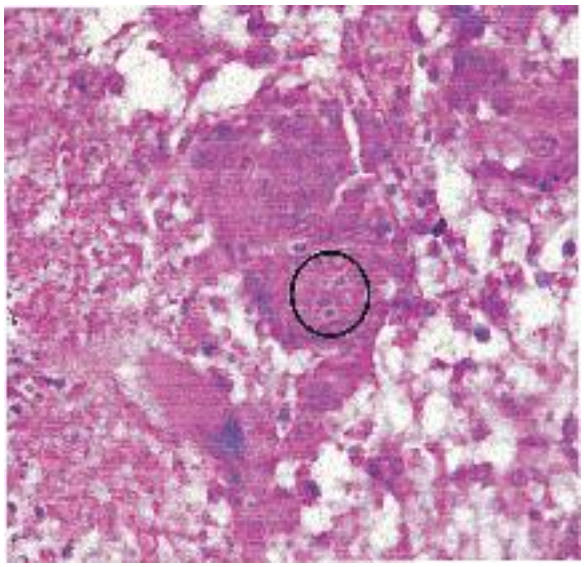

Fig. 2: Histopathological picture showing caseous necrosis with giant cells granuloma – AFB positive *Mycobacterium tuberculosis* (circled)

of the right nasal cavity and nasophranyx. The mass also involved the right ethmoid sinuses and the orbit, and it extended intracranially into the middle cranial fossa.

Endoscopic biopsy specimens were taken from the proliferative mass. Histopathology revealed that the mass contained granulomas with caseous necrosis as well as Langhans' giant cells and numerous epithelioid cells (Fig 2). Analysis of sputum for AFB was negative, and findings on chest x-ray were normal. The patient was started on standard four-drug antituberculosis therapy (rifampin, isoniazid, ethambutol, and pyrazinamide). After six months of follow-up, MRI revealed that the lesion had resolved completely. The vision showed dramatic improvement and without any assistance, the boy was able to see things clearly at a distance of three metres.

DISCUSSION

Nasal tuberculosis is a rare, chronic, granulomatous infection caused by *Mycobacterium tuberculosis*. The rarity of this disease can be explained by the protective functions provided by the ciliary action of the nasal mucosa, the bactericidal properties of the nasal secretions, and the protective mechanisms of the nasal vibrissae. The probable importance of an intact mucosal epithelium in providing protection against the infection has support from the observation of Abbot *et al* [7] who were able to isolate the tubercle bacilli from mouth washings of 44.9% of the patients with active pulmonary lesions. The infection can be introduced into the nose by inhalation of infected droplets or dust and by inoculation via the finger[8].

A recent review reports 36 cases published in the twentieth century showing a predominance of middle-aged women[9]. Our case was unusual in that it occurred in a boy. Nasal obstruction and rinorrhoea are the most frequent symptoms, although epistaxis, the presence of ulcerative lesions or recurrent polyps can be observed. Lesions are usually unilateral affecting the cartilaginous parts of the septum or the inferior turbinate. Culture of nasal secretions is usually negative and a biopsy with culture is necessary[10]. In our case, biopsy revealed caseating necrosis with acid fast bacilli on ZN staining.

Nasal tuberculosis is extremely rare[10] and other forms of granulomatous diseases must be considered first. In our patient, clinical findings (i.e., epistaxis and fever) and CT findings (i.e., an extensive bilateral nasal and ethmoidal mass with intracranial extension into the middle cranial fossa and involvement of the right orbit) suggested a malignancy. Special investigations may help to reveal diagnosis but are often unreliable. The least invasive investigation for diagnosis is tuberculin skin testing. The tuberculin skin test is usually positive in tuberculosis; however, a negative test result does not rule out the disease. In our case, the tuberculin skin test was highly positive. The erythrocyte sedimentation rate may be elevated, as in our case described, and thus it is a good therapeutic indicator but is not specific. Confirmation of the diagnosis can be made with the following criteria: (1) compatible histopathology appearance of biopsied tissue (granuloma with epithelioid cells), (2) demonstration of AFB on biopsy specimen, and (3) growth of *Mycobacterium tuberculosis* from the biopsy specimen[11,12]. However, initial microbiologic investigation with conventional acid-fast stains (e.g.,

Ziehl-Neelsen) and the fluorochrome procedure with stains such as auramine can be unreliable and are negative in up to 50% of cases. Culture of mycobacterium is time-consuming, requiring five to six weeks to produce results. The yield is also low. In the literature, cultures are reported to be positive in 50% to 70% of patients[13,14]. So the diagnosis is most often made by a combination of the clinical picture, histological findings, and response to anti-tuberculous medication.

Our patient did not exhibit any other symptoms that would have suggested a diagnosis of tuberculosis. Our final diagnosis was not established until we obtained the results of histopathology and other tests. The diagnosis was confirmed by the patient's rapid response to antituberculosis drug therapy. We found no evidence of immune-suppression.

After reviewing literature,` we came across only one more case report with similar presentation[15] and similar to that case, this case report brings forward the menacing nature of the disease and prepares us to view such presentation with tuberculosis in our mind while dealing with a case in a non immuno-compromised individual.

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Indian J Tuberc 2010; 57: 223-225

STATUS REPORT ON RNTCP*

Revised National TB Control Programme has achieved NSP case detection rate of 79% and treatment success rate of 87% at the national level during the second quarter, 2010. This quarter has seen one of the highest case detection rates at country level. The programme, while consolidating and sustaining its past achievements, is progressing well towards achieving the TB related Millennium Development Goals.

RNTCP performance in second quarter 2010

During the quarter, over 1.9 million suspects were examined, 258,742 sputum positive cases were diagnosed, and 416,738 TB cases were registered for treatment. The annualized total case detection rate is 149 cases per 100,000 population. With a total of 173,770 new smear positive cases being registered for treatment, the new smear positive TB case detection rate (annualized) for the second quarter 2010 is 79%. In addition to this, 99,693 new smear negative cases, 65,238 new extra pulmonary cases, 52,308 smear positive re-treatment cases and 23,316 re-treatment Others' were also registered for treatment in this quarter. The treatment success rate amongst the new smear positive PTB cases registered in the second quarter 2009 is 87% and the sputum conversion rate of patients registered during first quarter, 2010 is 90%. The default rates among NSP (5.7%), NSN (7%) and re-treatment cases (14.1%) continue to show the declining trend over the past several quarters.

Major activities during the quarter

Programme review

Joint Monitoring Review Mission

The programme was reviewed by a team of experts from World Bank, WHO, USAID, DFID, Global Fund, Clinton Foundation and Bill and Melinda

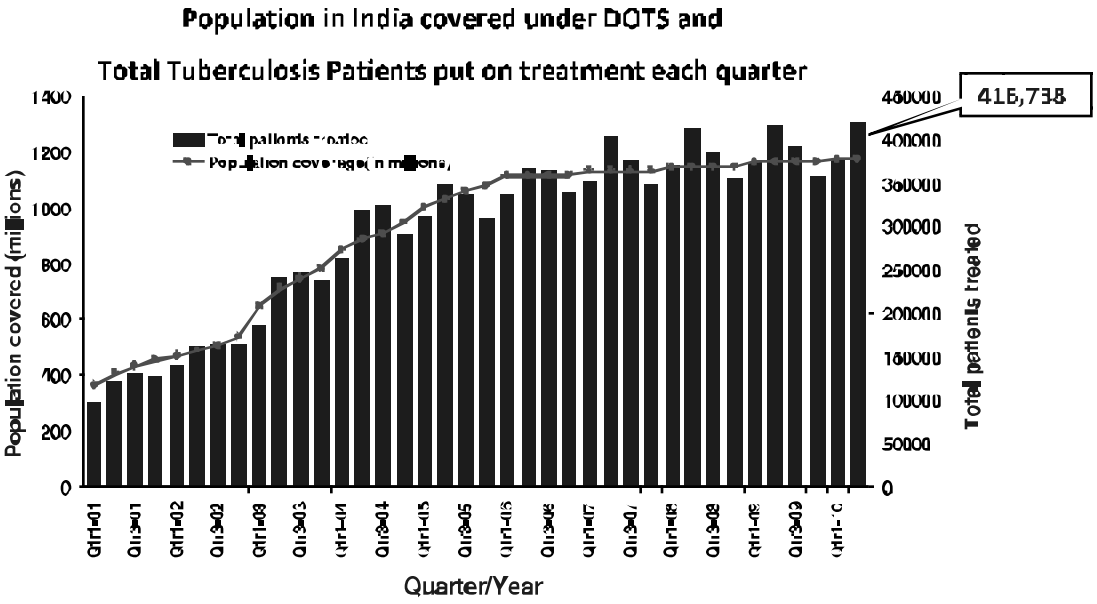

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Table: Performance of RNTCP Case Detection (2010, second quarter), Smear Conversion (2010, first quarter), and Treatment Outcomes (2009, second quarter)

State	Population (in lakh) covered by RNTCP[1]	Suspects examined per lakh population	No of Smear positive patients diagnosed[2]	Total patients registered for treatment[3]	Annualized total case detection rate	New smear positive patients registered for treatment	Annualized new smear positive case detection rate (%)		No of new smear negative cases registered for treatment	No of new EP cases registered for treament	% of new EP cases out of all new cases	No. of smear positive retreatment cases registered for treatment	3 month conversion rate of new smear positive patients	Cure rate of new smear positive patients	Success rate of new smear positive patients
Andaman & Nicobar	3	18	58	176	117	69	58	77%	31	47	37%	25	82%	80%	82%
Andhra Pradesh	840	154	20263	28869	138	17061	62	83%	6929	3297	14%	4139	91%	86%	88%
Arunachal Pradesh	2	29	535	751	239	313	19	05%	168	147	26%	84	93%	87%	85%
Assam	302	131	6470	10861	144	4623	61	82%	2792	1501	18%	1090	89%	83%	85%
Bihar	964	103	13175	22385	93	9783	41	54%	7204	1468	8%	2024	87%	80%	89%
Chandigarh	1	301	565	781	228	371	19	86%	139	257	38%	93	93%	91%	91%
Chhattisgarh	239	109	3592	7537	126	2961	49	62%	2864	975	11%	453	88%	82%	85%
D & N Haveli	3	162	74	105	125	36	43	53%	30	23	26%	17	85%	77%	77%
Daman & Diu	3	222	66	65	102	9	29	37%	3	18	36%	10	57%	77%	77%
Delhi	179	236	6830	13595	378	4057	90	95%	2695	5552	42%	1932	89%	85%	82%
Goa	17	154	291	499	116	185	44	55%	72	152	37%	60	87%	86%	86%
Gujarat	552	160	16958	20300	171	9517	65	89%	2979	2 0	19%	4368	90%	85%	85%
Haryana	250	181	7132	10855	177	7071	55	68%	2432	1929	21%	2038	90%	84%	85%
Himachal Pradesh	67	275	2722	4146	276	1548	22	97%	678	1030	32%	606	92%	85%	90%
Jammu & Kashmir	125	200	2370	3787	151	1517	5	67%	570	825	26%	397	91%	89%	90%
Jharkhand	320	127	6403	10917	141	4967	62	85%	3501	795	9%	850	92%	84%	90%
Karnataka	558	198	11525	17652	120	7193	49	65%	3687	3182	23%	2510	56%	70%	87%
Kerala	345	216	3 5	5290	72	2167	32	65%	121	284	25%	609	83%	83%	84%
Lakshadweep	1	125	3	4	27	2	11	14%	1	0	0%	1	0%	100%	100%
Madhya Pradesh	711	123	14546	23178	130	9478	53	67%	6790	2562	14%	3035	91%	85%	88%
Maharashtra	111	13	9426	51033	123	13040	47	59%	741	65 9	21%	3988	89%	84%	86%
Manipur	24	129	409	949	157	293	48	65%	301	177	23%	79	91%	82%	83%
Meghalaya	26	196	720	1343	207	456	70	94%	274	320	30%	164	86%	84%	86%
Mizoram	9	199	175	390	238	139	48	6 %	143	203	1%	8	89%	89%	90%
Nagaland	22	181	528	1086	195	375	67	90%	269	240	27%	119	93%	91%	92%
Orissa	407	122	8120	13727	133	6273	62	73%	2968	2447	2 %	1123	88%	83%	87%
Puducherry	13	376	555	105	122	168	50	0 %	91	71	23%	55	87%	89%	89%
Punjab	274	183	7400	12265	179	5142	75	79%	2259	2523	26%	1725	90%	86%	88%
Rajasthan	668	161	21204	32983	198	12678	76	93%	8597	4575	18%	3829	92%	85%	90%
Sikkim	6	336	205	183	319	134	89	118%	121	121	1%	71	86%	86%	86%
Tamil Nadu	670	297	11768	21184	126	8707	52	69%	5431	4025	22%	2355	90%	86%	87%
Tripura	36	145	537	769	86	403	45	60%	199	133	20%	80	90%	91%	91%
Uttar Pradesh	1973	161	49355	79 10	151	30740	59	73%	21758	0015	15%	10378	91%	86%	89%
Uttarakhand	98	212	3235	4461	182	1717	70	74%	989	736	21%	765	89%	81%	85%
West Bengal	887	153	18304	28367	128	12506	61	84%	4092	4564	21%	3326	88%	84%	85%
Grand Total	11767	161	258742	416738	142	173770	59	79%	99693	65238	19%	54308	90%	85%	87%

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

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

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

Gates Foundation from 17th to 28th May, 2010 with the principal objectives to review progress since the 2009 Joint Monitoring Mission with special emphasis on long term financing of RNTCP; procurement, distribution and quality assurance of anti-TB drugs; laboratory expansion for diagnosis/follow up of MDR-TB; MDR-TB treatment; human resource development; and innovations for TB prevention, diagnostic and treatment. The mission conducted detailed discussion at Central TB Division, visited the states of Madhya Pradesh, Rajasthan, Kerala and provided useful recommendations in those thematic areas for the programme to consider.

RNTCP was reviewed in detail by Joint Secretary (PH) on 17th and 18th June 2010 with State TB Officers and RNTCP Consultants. The major thrust given in all this review is on the importance of Universal access for TB care. Every TB patient in the country should have access to early case detection and standardized care in all health care facilities. Strategies for the universal access for TB care were developed in the meeting and are being implemented in all states.

Progress in accreditation of Intermediate Reference Laboratories (IRL)

The programme is in the process of establishing a network of about 43 accredited Culture and Drug Susceptibility testing (DST) Laboratories across the country in a phased manner for diagnosis and follow-up of MDR TB patients. The State Culture and DST Laboratories at Gujarat, Maharashtra, Andhra Pradesh, Delhi, Kerala, Tamil Nadu, Rajasthan, West Bengal, Orissa and Jharkhand have been accredited. State Culture and DST Laboratories of Haryana and UP are in the advanced stages of proficiency testing and the laboratories of other states are under various stages of the accreditation process. To supplement and support the state laboratory network, the programme is also involving Mycobacteriology laboratories of Government Medical Colleges as well laboratories in the NGO and Private Sector. Till date, four laboratories in other sectors (CMC-vellore, PD Hinduja Hospital –Mumbai, BPRC-Hyderabad and SMS Jaipur) have been accredited and about 11 such laboratories have applied for accreditation. Apart from these four Govt medical college laboratories are also in the accreditation process, AIIMS New Delhi, KGMU Luknow, and PGI Chandigarh.

Progress in the DOTS- Plus services for MDR TB cases

DOTS Plus services for management of MDR TB are now available in 125 districts covering a population of 260 million in 10 states. Till date, a total of around 2300 MDR-TB patients are on treatment in these states. Other states are in various stages of preparatory activities for rolling out DOTS-Plus services.

Air-borne infection control

RNTCP has facilitated in drafting National Guidelines for Air-borne infection control and is piloting in three states, West Bengal, Gujarat and Andra Pradesh. In this quarter, air-borne infection risk assessment visits were conducted in 11 facilities in West Bengal and nine facilities in Gujarat and air-borne infection control capacity building workshop was conducted in Andhra Pradesh.

Progress in partnerships

CBCI launched the Global fund RCC project in an additional eight states thus expanding the project from 11 to 19 states and similarly IMA has also expanded the project to 16 states.

Short Communication

AWARENESS, ATTITUDE AND TREATMENT SEEKING BEHAVIOUR REGARDING TUBERCULOSIS IN A RURAL AREA OF TAMIL NADU

Malini Kar[1] and M. Logaraj[2]

(Received on 23.3.2010; Accepted on 6.9.2010)

Summary: A population based cross-sectional study was carried out to assess the awareness, attitude, and treatment seeking behaviour regarding TB in rural Tamil Nadu. Out of 1985 people interviewed, 56% had heard of TB, but 80% were not aware of the cause and mode of spread of TB. Television was reported to be the main source of information (45%). Only 34% people were aware that treatment for TB was available free of cost. Less than 10% people felt the need to maintain confidentiality, if contracted TB. More than 80% people preferred to visit Government hospital, if developed TB, whereas 54% actually sought treatment from government hospital for cough of more than three weeks. ***[Indian J Tuberc 2010; 57:226-229]***

***Key words*:** Awareness, Attitude, Treatment seeking behaviour, Tuberculosis, Rural India

INTRODUCTION

India has the highest number of TB cases in the world[1]. After implementation of Revised National TB Control Programme using DOTS strategy, cure rate has dramatically improved from 30% to more than 85% and has been consistently maintained at a satisfactory level. However, attainment of minimum level of case detection rate of 70% in order to have any long term impact in terms of reduction in incidence and prevalence rates has been proved to be a hard task[2]. Information, Education, and Communication (IEC) is an integral and important strategy of the programme to create awareness among public, health care providers and policy makers. As the programme advocates passive case detection method, level of awareness regarding the common symptoms of TB plays the key role in timely seeking treatment. Similarly, the message regarding availability of "free diagnosis and treatment facility for TB" in government and selected private health centres needs to be widely known by general public, if we expect them to come forward to avail the facility.

Tamil Nadu was among the first few states in India, where service delivery under RNTCP started in the first phase of the programme. The entire State was brought under RNTCP coverage by 2001-02. The present study was carried out to assess the level of awareness, attitude and treatment seeking behaviour regarding tuberculosis in a rural area of Tamil Nadu, keeping in mind the parameters related to improved case detection.

MATERIAL AND METHODS

The study was carried out in the field practice area of Rural Health Centre, Chunampet, district Kancheepuram, Tamil Nadu, run by Pondicherry Institute of Medical Sciences, during February-March 2008. The district implemented RNTCP in December 2000. Eight villages were selected from the surrounding area based on proximity to the health centre. The mean distance of the villages was five kms from the centre. House-to-house survey was carried out using a pre-tested, pre-designed, semi-structured questionnaire. The

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Table 1: Source of information regarding Tuberculosis (n=1105) (Multiple sources reported by some respondents)

Source of Information	No.	%
Television	500	45%
Friends	276	25%
Health care providers	167	15%
Family members	111	10%
School	104	9%
Newspapers	73	7%
Radio	60	5%

proforma included questions on demography, socio-economic status, knowledge, attitude and practices about TB. All available persons more than 15 years were included in the study. Data was compiled and analyzed through computer using the "SPSS" statistical package.

RESULTS

A total of 1985 people were interviewed, of whom 917 (46%) were males and 1068 (54%) were females. Thirty nine per cent of the study population was illiterate. Agriculture was the chief occupation (45%) among males; whereas majority (49%) of females were housewives. Majority were Hindu (94%). More than 70% of the people belonged to lower income group.

Awareness and Knowledge about TB: Forty four per cent (880/1985) of the respondents said they had never heard of TB. Out of the 1105 people who had heard of TB, maximum (45%) reported television as one of the sources of information. Multiple sources were reported which are enlisted in Table-1. Regarding knowledge about mode of spread of the disease, only 20% replied cough or sputum as the mode of spread. The rest 80% didn't have any knowledge or wrong knowledge about spread of TB. Literacy status was the key factor in determining level of awareness about TB.

Attitude regarding seeking treatment and maintaining confidentiality for TB: Eighty-five per cent respondents said they would prefer to go to a government hospital, if suspected to be having TB. When asked whether they would like to maintain confidentiality if contracted TB, 92.7% said "No". The rest mentioned "the fear of isolation or discrimination" as the main reason for maintaining confidentiality. Interestingly, there was no

Table 2: Duration of cough and treatment seeking behaviour of the respondents

Duration of cough	Govt. Hospital	Private hospital	Home remedy/ self treatment	Total
<1 week	24 (26%)	13 (14%)	54 (59%)	**91 (100%)**
1-2 weeks	33 (56%)	15 (25%)	11 (19%)	**59 (100%)**
2-3 weeks	11 (61%)	2 (11%)	5 (28%)	**18 (100%)**
>3 weeks	25 (38%)	21 (32%)	19 (29%)	**65 (100%)**
Total	93 (40%)	51 (22%)	89 (38%)	**233 (100%)**

significant difference in the attitude among males and females regarding keeping TB confidential. However, more literates wanted to keep TB confidential compared to illiterates. The difference was statistically significant.

Treatment seeking behaviour for cough: The prevalence of chest symptomatics, i.e. having cough for three weeks or more was 3.3% (n=65) during the survey. Twenty nine percent (19 of 65) of those with cough for more than three weeks did not seek treatment. Lack of time and money were the important reasons stated for not seeking treatment. Out of those who sought treatment (n=46), 54% (n=25) went to a government hospital and the rest 46% to private hospitals (Table-2). Twenty five (1.3%) people out of the study population reported as being ever diagnosed having TB.

DISCUSSION

The mass survey carried out by Central TB Division, Ministry of Health, Govvernment of India, reported poor level of awareness among general population and very poor among disadvantaged section of the society[3]. Literacy has been identified as the key deciding factor for level of awareness. The KAP study among sandstone quarry workers in Rajasthan, conducted by Yadav *et al*, showed literate people having significantly higher level of awareness and knowledge regarding TB[4]. Devey reported that only 21% of people from Northen part of Bihar knew how TB is spread. The level of knowledge was determined by educational and economic status of the person[5]. However, the study conducted in rural Delhi in 2001 showed encouraging results with more than 95% participants being aware of cause of TB.[6] It is encouraging from the present study that people no longer want to keep TB confidential. The study conducted in 1997 by National TB Institute, Bangalore, also did not find social stigma attached with TB in the study area[7]. Several studies have confirmed that education and economic status are important parameters determining treatment seeking behaviour of TB patients[8,9]. The study conducted by Grover *et al* showed people from rural area and belonging to lower socio-economic status were significantly associated with delay in contracting treatment for tuberculosis[10].

One of the important methods to identify the deficiencies in RNTCP, and plan for future improvement is by carrying out periodic KAP surveys. World Health Organization recognizes the importance of tuberculosis-related knowledge, attitude and practice surveys in advocacy, communication and social mobilization strategy planning[11].

The results of this study indicate that different IEC activities need to be developed in order to create awareness, especially among illiterates. As literacy rate and economic status of rural population is still low, innovative methods have to be used to create awareness among these people. Important messages like "to seek treatment for cough of more than three weeks (now two weeks)" and "free availability of TB diagnosis and treatment", etc., should be spread using different communication channels in order to increase case-detection rate. Active case detection method may be experimented in selected areas where cure rate has been achieved and maintained consistently for several years.

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SIXTY FIFTH NATIONAL CONFERENCE ON TUBERCULOSIS AND CHEST DISEASES - BENGALURU – JANUARY, 2011

The 65th National Conference on Tuberculosis and Chest Diseases (NATCON 2010), under the joint auspices of the Tuberculosis Association of India and the Karnataka State Tuberculosis Association, will be held in Bengaluru from 10th to 12th January, 2011, at NIMHANS CONVENTION HALL, Hosur Road, Bengaluru-560 029. Registration form, Hotel accomodation form, etc., can be downloaded from the website given below.

Conference Secretariat

KARNATAKA STATE TUBERCULOSIS ASSOCIATION,
3, Union Street, Infantry Cross Road,
Bangalore 560001.
Telephone: 080 22862387.
Mobile Nos.: 09448062579/09448042579;
Website: www.kstbassociation.org.

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ABSTRACTS

Comparison of MGIT 960 and pyrazinamidase activity assay for pyrazinamide susceptibility testing of *Mycobacterium tuberculosis*.

Babita Sharma, Nita Pal, Bharti Malhotra, Leela Vyas and Suman Rishi. *Indian J Med Res* 2010; **132**: 72-6.

Pyrazinamide is an important front line antimycobacterial drug, which is also being used in the treatment of multi drug resistant tuberculosis along with second line drugs in DOTS plus programme. Conventional testing of pyrazinamide on solid medium is difficult as it is active at acidic *pH*. Therefore, there is a need for a rapid and simple method for susceptibility testing of pyrazinamide. This study was carried out to compare pyrazinamide susceptibility testing by MGIT 960 and two rapid pyrazinamidase activity tests. Pyrazinamide susceptibility was tested in 136 clinical isolates of *Mycobacterium tuberculosis* by MGIT 960 and pyrazinamidase activity was tested by classical Wayne's method and modified PZase agar method. There was 88.9 per cent concordance between MGIT 960 and classical Wayne's method and 93.38 per cent with modified method for pyrazinamidase activity. Using MGIT 960 results as gold standard the sensitivity and specificity of Wayne's method was 88.15 and 90 per cent respectively and that of modified method was 89.4 and 98.3 per cent. Our study demonstrates that the modified pyrazinamidase activity test can be used as a screening test to detect resistance to pyrazinamide specially in resource limited settings but confirmation of susceptibility should be done by standard methods like MGIT 960.

Ultrasonography for diagnosis of abdominal tuberculosis in HIV infected people.

Dipti Agarwal, Shamrendra Narayan, Jaya Chakravarty and Shyam Sundar. *Indian J Med Res* 2010; **132**: 77-80.

There is an increasing incidence of abdominal tuberculosis with the advent of HIV infection. This study was aimed at determining the pattern of presentation of abdominal tuberculosis on Ultrasonography (USG) in HIV positive patients. This retrospective study was carried out at the ART Centre, Sir Sunderlal Hospital, Banaras Hindu University, Varanasi, between March 2005 to July 2007. HIV positive patients (n=2453) with prolonged fever, abdominal pain/distension, altered bowel habits and diarrhoea underwent ultrasonography for tuberculosis of abdomen. The different ultrasonological findings in abdominal tuberculosis were noted. CD 4 counts of these patients were also recorded. Of the total 2453 patients, 244 showed findings suggestive of abdominal tuberculosis. Lymphadenopathy with predominantly hypoechoic/necrotic echotexture was seen in 158/244 (64.8%) patients. Splenomegaly was seen in 68 patients with 61 of them (89.7%) showing multiple hypoechoic lesions in the parenchyma. 53 of 244 (21.7%) showed extensive abdominal involvement. Liver enlargement was seen as a part of extensive abdominal involvement. A total of 203 patients completed antitubercular treatment, of which 198 (97.5%) showed resolution of lesions in *USG*. CD4 counts in patients with extensive abdominal involvement were lowest compared to CD4 count in patients with others *USG* findings. Ultrasonological findings like lymphadenopathy (e"1.5 cm) with hypoechoeic/ necrotic echotexture, hypoechoic splenic lesions and extensive abdominal involvement in HIV infected patients may be suggestive of abdominal tuberculosis.

Evaluation of risk factors for antituberculosis treatment induced hepatotoxicity.

Rohit Singla, Surendra K. Shanna, Alladi Mohan, Govind Makharia, V. Sreenivas, Brajesh Jha, Sanjeev Kumar, Pawan Sarda and Sarman Singh. *Indian J Med Res* 2010; **132**: 81-6.

Antituberculosis (anti-TB) Drug Induced Hepatotoxicity (DIH) is the most common side effect leading to interruption of therapy. Wide

variations have been found in the reported incidence of hepatotoxicity during short-course chemotherapy. Several risk factors for hepatotoxicity have been suggested in previous studies. We undertook a prospective case-control study to assess the role of these putative risk factors in the development of DIH in patients receiving anti- TB treatment. One hundred and seventy five consecutive cases with a diagnosis of anti-TB DIH were compared with 428 consecutive controls who took anti-TB drugs for the full duration of chemotherapy without clinical or biochemical evidence of hepatitis. Cases positive for markers of acute viral hepatitis were carefully excluded. Cases and controls were compared with respect to age, sex, site of tuberculosis, radiological extent of disease on chest radiograph, body mass index (BMI), mid-arm circumference: (MAC) and liver function at baseline which included serum bilirubin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), serum total protein and serum albumin. Univariate logistic regression revealed that the risk of developing DIH was greater in older patients. Significantly greater percentage of cases had extrapulmonary tuberculosis (TB) *(P<0.01)*. Also, a significantly higher percentage of cases had moderate to far advanced disease severity on chest radiograph *(P<0.01)*. On multivariate logistic regression, the adjusted odds were significant (P<0.01) for age >35 yr, MAC <20 cm and hypoalbuminaemia (albumin <3.5 g/dl). Older age, poor nutritional status including baseline hypoalbuminaemia were independent predictors of occurrence of anti-TB DIH. Clinicians should be vigilant for occurrence of hepatotoxicity in this high risk group.

Comparison of Tuberculin Skin Testing and T-SPOT. TB for Diagnosis of Latent and Active Tuberculosis.

Hulya Simsek, Sibel Alpar, Nazire Ucar, Funda Aksu, Ismail Ceyhan, Aysegul Gozalan, Salih Cesur and Mustafa Ertek. *Jpn J Infec Dis* 2010; **63:** 99-102.

The T-SPOT. TB test does not cross-react with Bacilus Calmette-Guerin or most non-tuberculosis mycobacterium species, and is based on IFN-ã responses to *Mycobacterium tuberculosis-specific* antigens. The objective of this study was to compare tuberculin skin test (TST) with T-SPOT. TB results used in the diagnosis of active tuberculosis (TB) as well as latent tuberculosis infection (LTBI). A total of 136 subjects participated in three different groups (47 patients with active pulmonary TB, 47 healthy persons without *M. tuberculosis* exposure, and 42 hospital members with a history of close contact with active TB patients). The T-SPOT. TB sensitivity (83.0%) and the negative predictive value (NPV) (82.6%) in the diagnosis of active TB were significantly higher than those of TST. The sensitivity and NPV of the TST were 38.3 and 60.8%, respectively. The T-SPOT. TB specificity (80.9%) and positive predictive value (81.3%) were lower than those of TST (95.7 and 90.0%, respectively). The performance of T-SPOT. TB and TST for diagnosing LTBI was the same (54.8%). T-SPOT. TB was superior in terms of sensitivity (83.0%); TST detected only 18, whereas T-SPOT. TB test detected 39 out of 47 patients with active TB. T-SPOT. TB is thought to have better performance than TST due to false-negative results in diagnosing active TB. However, it is considered that large prospective longitudinal studies are needed for diagnosing LTBI.

Added value of bleach sedimentation microscopy for diagnosis of tuberculosis: a cost-effectiveness study.

M. Bonnet, A. Tajahmade, P Hepple, *et al*. *Int J Tuberc Lung Dis* 2010; **14(5)**: 571-77.

Bleach sedimentation is a method used to increase the diagnostic yield of sputum microscopy for countries with a high prevalence of human immunodeficiency virus (HIV) infection and limited resources. The objective of the study was to compare the relative cost-effectiveness of different microscopy approaches in diagnosing tuberculosis (TB) in Kenya. An analytical decision tree model including cost and effectiveness measures of 10 combinations of direct (D) and overnight bleach (B) sedimentation microscopy was constructed. Data were drawn from the evaluation of the bleach sedimentation method on two specimens (first on

the spot [1] and second morning [2]) from 644 TB suspects in a peripheral health clinic. Incremental cost per smear-positive detected case was measured. Costs included human resources and materials using a micro-costing evaluation. All bleach-based microscopy approaches detected significantly more cases (between 23.3% for B1 and 25.9% for B1+B2) than the conventional D1+D2 approach (21.0%). Cost per tested case ranged between respectively •2.7 and •4.5 for B1 and B1+D2+B2. B1 and B 1 + B2 were the most cost-effective approaches. D1+B2 and D1+B1 were good alternatives to avoid using approaches exclusively based on bleach sedimentation microscopy. Among several effective microscopy approaches used, including sodium hypochlorite sedimentation, only some resulted in a limited increase in the laboratory workload and would be most suitable for programmatic implementation.

Baseline sputum time to detection predicts month two culture conversion and relapse in non-HIV-infected patients.

A.C. Hesseling, G. Walzl, D.A. Enarson *et al*. *Int J Tuberc Lung Dis* 2010; **14(5)**: 560-70.

Few biomarkers are available to identify tuberculosis (TB) patients at risk of delayed sputum conversion and relapse. The objective of the study was to investigate whether baseline pre- treatment time to detection (TTD) of culture predicted 2-month bacteriological conversion and TB relapse. A total of 263 non-HIV-infected smear-positive previously untreated pulmonary TB patients were prospectively followed from diagnosis until treatment outcome after 6 months' treatment and TB recurrence within 24 months. The median TTD was 3 days (range 1-17). Of 211 (80.2%) patients with favourable treatment outcome, 22 (10.4%) had recurrence, while 12 (5.7%) had confirmed relapse. Culture conversion at 2 months was associated in univariate analysis with the presence and number of cavities, extensive parenchymal involvement, male sex, sputum smear grading and TTD. In multiple logistic regression, TTD or smear grading and extensive parenchymal involvement both predicted month 2 conversion. Relapse was predicted by TTD, sex, body mass index, smear grading and number of cavities in univariate analysis, and in multivariate regression by TTD and sputum smear grading. Baseline TTD and smear grading predicted month 2 culture conversion, relapse and also recurrence. These markers may be useful to identify non- HIV-infected patients at risk of recurrence, and may be relevant in clinical trials.

Risk of tuberculosis in public transport sector workers.

O.J. Horna Campos, A. Bedoya-Lama, N.C. Romero-Sandoval and M. Martin-Mateo. *Int J Tuberc Lung Dis* 2010; **14(5)**: 714-19.

Delays from symptom onset to the diagnosis and treatment of smear-positive pulmonary tuberculosis (TB) produces possible new cases in persons in close contact with TB cases, especially in confined spaces such as overcrowded public transport, which puts other users and transport workers at risk. The objective of the study was to estimate TB incidence rates in patients of a health micro-network, and the percentage of transport sector workers among TB and multidrug-resistant TB (MDR-TB) patients. Crude and indirect standardised incidence rates of TB were calculated from an exhaustive analysis of all clinical histories of incident patients in a health micro-network between 1 January 2007 and 30 June 2008. The percentage of transport sector workers and the association between MDR- TB and working in the transport sector were analysed. Standardised incidence rates for transport sector workers are 2.7-4.5 times higher than those in the total working-age male and global population of the micro-network studied. The association between TB and transport occupation and MDR- TB and transport occupation is high (respectively OR 3.06, 95%CI 2.2-4.2 and OR 3.14, 95%CI 1.1-9.1). These results indicate that the use of informal public transport is a risk factor for TB infection and an occupational risk in countries with characteristics similar to those in Peru.

LIST OF REVIWERS

Agarwal, Nishi, *Delhi*
Agarwal, Upasna, *Delhi*
Arora, V.K *Delhi*
Banerji, D. *Delhi*
Banavaliker, J.N. *Delhi*
Bedi, R.S. *Patiala*
Behera, D. *Delhi*
Chadha, V.K. *Bangalore*
Chakraborty, A.K, *Bangalore*
Challu, V.K. *Bangalore*
Chauhan, L.S. *Delhi*
Chhabra, S.K. *Delhi*
Chopra, K.K. *Delhi*
Gaur, S.N. *Delhi*
Geetha Ramachandran, *Chennai*
Gopi, P.G. *Chennai*
Gupta, K.B. *Rohtak*
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Hanif, M. *Delhi*
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Jawahar, M.S. *Chennai*
Jain, Nirmal Kumar, *Jaipur*
Jain, V.K., *Rohtak*
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Vijayan, V.K. *Delhi*
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Wares, D.F. *U.K.*
Wilson, Nevin, *Delhi*

(Names are in alphabetical order)

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Obituary

(1928 – 2010)

The Tuberculosis Association of India places on record its deep sense of sorrow and profound grief on the sad demise of its senior Vice-Chairman (OR) and Editor of the *Indian Journal of Tuberculosis* Dr. Man Mohan Singh on 23rd August, 2010.

Born on 25.8.1928 in Lucknow, he did his M.B.B.S. from the prestigious King George's Medical College in 1951, Diploma in Tuberculosis in 1952 and MD in tuberculosis in 1954 at Lucknow. He then made Delhi as his "Karambhoomi". He was the First TB Control Officer of Delhi, Medical Superintendent, Rajan Babu TB Hospital, Delhi and Director, New Delhi TB Centre.

A doyen of tuberculosis and a stalwart among tuberculosis workers, Dr. M.M. Singh had to his credit many awards and recognitions of the Tuberculosis Association of India (TAI), served on its various committees and contributed a lot to TAI. He was the pillar of Delhi TB Association, President of NCCP and got the life time achievement award of NCCP. He was the founder President of JICA. He was a renowned physician with full command on the subject and was always helpful to his colleagues, students and the patients. He was a man of strong personality and always stood for the good causes which he thought were right. He devoted his time in philanthropic activities and dedicated his whole life to the cause of tuberculosis. He had been associated with many philanthropic organizations in various capacities.

His demise has created a void which is difficult to fill. The Tuberculosis Association of India conveys its deep condolences to the bereaved family and may his soul rest in eternal peace.