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Incidence of Multidrug-Resistant (MDR) and Extensively drug Resistant (XDR) Tuberculosis among Different age Groups in Tertiary Care Hospitals of Chandigarh, India

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ABSTRACT: Chandigarh has been adjudged among the top five performing states and union territories in the country by TB India-2008 RNTCP (Revised National Tuberculosis Control Programme) status report, brought out by the Union Health Ministry. In controlling TB, Chandigarh is now at par with Delhi, Rajasthan, Gujarat and Arunachal Pradesh. According to National Rural Health Mission, in 2008, 13,937 patients were examined for sputum diagnosis, out of which 1,793 were found positive and 837 new smear positive patients were put on treatment. The other smear positive patients were either referred to other states or were treated under other categories of treatment. The new sputum positive detection rate is 84 per lakh of population in Chandigarh. Up to December, 2008, 15,123 patients were put on treatment. In calendar year 2008, the total annual detection rate was 243 per lakh. There were only two per cent death among 2400-odd patients put on treatment in one year, two per cent failure rate and three per cent defaulter rate, the lowest in the country. A total of 910 cases of pulmonary tuberculosis were enrolled over four years (2008-2012). Among these, cases of MDR-TB and XDR-TB were meticulously studied for drug susceptibility, treatment, adverse effects profile and overall survival. Fifty-two (5.7%) cases of MDR-TB were identified, among which eight (15.3%) were diagnosed as XDR-TB on the basis of drug susceptibility testing, using the prescribed definition. The cases were sensitive to 2, 3, 4, 5 and more than 5 drugs in almost equal proportions. Thirty-seven (71.1%) cases were successfully cured; eleven (21.1%) patients died; and only four (7.6%) cases defaulted, indicating overall satisfactory adherence to treatment. For effective treatment of MDR-TB and XDR-TB, early case detection, improved laboratory facilities, availability of appropriate treatment regimens, and financial assistance in resource-limited settings through effective political intervention are necessary for better patient adherence and overall cure.

Key words: Tuberculosis, multidrug-resistant tuberculosis, extensively drug resistant tuberculosis, drug susceptibility testing.

INTRODUCTION

Tuberculosis remains one of the major public health problems in India. It has been estimated that about 30% of the world's tuberculosis patients are residing in India. Since the control measures for tuberculosis such as BCG vaccination and chemoprophylaxis seem to be unsatisfactory, treatment with anti-tuberculosis drugs becomes inevitable. In recent years, the treatment of tuberculosis has been threatened by the increasing number of patients with drug resistant tuberculosis. Although the phenomenon of drug resistance to *Mycobacterium tuberculosis* was observed even in the early days of streptomycin usage, the current threat is due to emergence of strain resistant to potent bactericidal anti-tuberculosis drugs such as isoniazide (H) and rifampicin (R) which are used in the TB programmes.

Multidrug-resistant tuberculosis has evolved as a significant public health problem worldwide and an obstacle to the effective global control of TB in recent years (Arova *et al* 2007 & Mak *et al* 2008). The incidence has an upward trend. According to estimates of the World Health Organization (WHO) Stop TB Department, the number of incident cases (including new and re-treatment cases) occurring worldwide in 2003 alone were to the extent of 4,58,000 (95% confidence limits, 3,21,000-16,89,000) with a projected figure of prevalent cases two to three times higher (WHO/HTM/TB/2006).

Per recent published reports from India, MDR-TB has been found in 3% of new and 12% of treated patients (Arova *et al* 2007). Other studies in India have also shown that the rates of acquired drug resistance are invariably higher than the rates of primary drug resistance (Arora and Visalakshi 2003); however, there are no published reports from the Punjab state so far. More recently, since March 2006, extensively drug-resistant tuberculosis (XDR-TB) has become the most alarming issue in the international effort to control TB in view of the poor treatment options and poor outcomes in those who are affected in both developing countries as well as in the developed world(Raviglione 2008) .One report published in 2007 from Mumbai, India, observed 9-11% of MDR-TB having XDR-TB cases, although the expected figures would be higher, as there is lack of culture facilities (Udwadia 2008). Subsequently in 2008, our report of 15.3% of XDR-TB among the MDR cases was published (Bikram *et al* 2008) .The present study of MDR-TB is the first of its kind from the Punjab state of India.

Table 1. Demographic profile of Mycobacterium tuberculosis in 52 patients with MDR-TB.

Age(Mean)	**14-70(38)**
Gender-Male/Female	29.23
Duration of symptoms (months)	23(1-84)*
Present Symptoms	
Cough	46(90.01)
Fever	29(55.7)
Hemoptysis+	28(53.8)
Other constitutional symptoms+	32(61.5)
Chest Radiographic Features	
Combinations of infiltrates, cavities and fibrotic areas+	37(71.1%)
Cavities+	19(36.5)
Pneumothorax+	11(21.1)
Infiltrates+	11(21.1)
Pleural effusion with infiltrates+	9(17.3)
Consolidation+	8(15.3)

*data expressed as median (range) +, data expressed as number (%)

Table 2. Drug susceptibility profile of 52 MDR-TB cases.

Resistance	Males	Females	Total (%)
2 drugs (HR)	4	3	7(13.4)
3 drugs:			
HRZ	3	3	6(11.5)
HRE	1	4	5(9.6)
HRS	2	1	3(5.7)
HREto	0	2	2(3.8)
4 drugs			
HRZS	4	6	10(19.2)
HRSE	1	2	3(5.7)
HRCs Cfz	2	0	2(3.8)
HRSOfx	0	1	1(1.9)
5 drugs			
HRZSE	2	0	2(3.8)
HRSEAm	1	1	2(3.8)
HRSEPAS	0	1	1(1.9)
>5 drugs	5	3	8(15.3)

H,isoniazid ;R,rifampicic; Z,pyrazinamide; E,ethambutol; S,streptomycin; Ofx,Oflaxacin; Cs,Cycloserine; Eto,ethionamide; Cfz,Clofazimine; Am,Amikacin; PAS.para-aminosalicylic acid.

Table 3. Prevalence of MDR-TB isolates among new cases in India [15].

Place	Study period	No. of isolates tested	% age of MDR-TB isolates
Gujarat	1983-86	570	0
North Arcot district	1985-89	2779	1.6
Pondicherry	1985-91	2127	0.7
Bangalore	1980	436	1.1
Bangalore	1985-86	588	1.4
Kolar	1987-89	292	3.4
Jaipur	1988-91	1009	0.8
Tamil Nadu	1997	384	3.4
North Arcot district	1999	282	2.8
Raichur district	1999	278	2.5
Chandigarh (present study)	2008-2012	910	5.7

MATERIALS AND METHODS

Study Population

This was a prospective, longitudinal, hospital-based clinico-microbiological observational study conducted at the Hospital associated with the Government Medical College Chandigarh, Punjab, India, where all the suspected MDR-TB cases from the Govt.Medical College & Hospital (a tertiary health care centre), and all the peripheral and central hospitals of the state are referred for evaluation and management. A prospective analysis was performed regarding the treatment outcome of 910 cases of pulmonary tuberculosis registered under RNTCP (Revised National Tuberculosis Programme) in March 2008 to February 2012.

Data Collection

Data was collected by analysis of the treatment cards of patients enrolled for directly observed treatment short-course (DOTS) at each visit to the hospital. All registered MDR TB cases were treated with the appropriate dosage of drugs per the sensitivity panel and followed up regularly.

Diagnostic Methods

Diagnosis was made on the basis of clinical features, chest radiography, sputum microscopy, and other supportive laboratory parameters including Monteux text, ELISA, polymerase chain reaction, and adenosine deaminase levels in pleural fluids. Among 910 cases, 386 (42.4%) were sputum smear positive. Cases were put on the recommended anti-tubercular treatment regimen. Those cases who had treatment failure were subjected to sputum culture and drug susceptibility tests. Sputum culture and drug susceptibility testing were conducted in all such cases in Laboratory, Department of Microbiology, Govt.Medical College, Chandigarh by using the BACTEC MGIT960 instrument optimized for rapid detection of mycobacteria from the clinical specimens. Samples collected from patients were processed and inoculated into BBLMGIT 7 ml tubes at 37^{o}C. The culture vials contained a fluorescence sensor that responds to the concentration of oxygen in the culture medium. The instrument's photo detectors measured the level of fluorescence which corresponds to the amount of oxygen consumed by the organisms. In cases of positive cultures, susceptibility testing for the isolates was done by 5649-AFB susceptibility: SIREP panel by Radiometry.

The MDR-TB cases were treated with drugs per culture and sensitivity. The intensive phase was extended until the negativity of sputum smears and second-line drugs (per the sensitivity panel) in the continuation phase were given for at least 18 months after smear and culture conversion. Their overall course including adverse effect profile was meticulously monitored.

Estimation of thyroid functions and serum uric acid levels was conducted in selected cases in whom the illness was suspected to be due to the effect of drugs. Those patients for whom prior estimation of these biochemical tests was not done were excluded from the study.

Statistical Analysis

The clinical information and laboratory data were expressed and analyzed on a per patient basis. For comparisons between groups, paired and unpaired students t test (Microsoft Excel) were applied using a significance level of $p = 0.05$.

RESULTS

Overall there were 910 cases of PTB in the study population. Among these 529 (58.1%) were males and 381 (41.8%) females in the age group of 14 to 85 (mean + SD, 39 + 4.7) years. Patients were given appropriate treatment regimens of anti-tuberculosis therapy until 2006, and subsequently using the directly observed treatment short-course (DOTS) strategy with standardized regimens per the guidelines of the Revised National Tuberculosis Control Programme (Arova *et al* 2007). Out of this population, three patients who had mono-resistance to either H or R were excluded, and only 52 cases were enrolled as MDR-TB according to the prescribed definition. The number of males enrolled was relatively higher than that of females. Cough was the most common symptom. The most interesting radiographic finding was the presence of pneumothorax in 11% of the cases. Smear positive cases of PTB with pneumothorax had more chances of having MDR-TB than those without pneumothorax. After clinical cure, chest radiographs of 11 (21.1%) patients were normal, while in others fibrocavitatory lesions persisted. Overall, 21 (40.3%) cases had co-morbid illnesses (which included risk factors as well) as follows: 9 (17.3%) associated chronic obstructive pulmonary disease; 4 (7.6%) diabetes mellitus; 3 (5.7%) bronchial asthma; 2 (3.8%) chronic renal disease; 1 (1.9%) human immunodeficiency virus (HIV); one (1.9%) chronic liver disease; and one (1.9%) cystic bronchiectasis.

The study identified 19 (36.5%) cases with initial resistance and 33 who had interrupted anti-tuberculosis therapy (63.4%) with secondary resistance. Results of the drug-susceptibility testing (Table 2) showed highest resistance to four drugs (53%). Lowest resistance was to para-aminosalicylic acid and amikacin, although the sensitivity testing to these drugs was performed in only a few cases.

Out of 52 patients of the study group, 12 (23%) patients achieved smear conversion within 2 months, 18 (34.6%) in 3 months, 9 (17.3%) in 4 months and 5 (9.6%) in 5 months. Eight patients with XDR-TB per the susceptibility testing did not convert to sputum negative by the end of six months. Per sputum culture, 3 (5.7%) cases became culture negative at the second month of treatment, whereas 20 (38.4%), 15 (28.8%), 4 (7.6%) and 2 (3.8%) patients achieved culture conversion at 3, 4, 5 and 6 months of treatment respectively.

Minor adverse effects such as nausea, vomiting, taste disturbances, itching, and dyspepsia, which were effectively managed with symptomatic treatment, were observed in 36 (69.2%) patients. The most striking adverse effect was hypothyroidism observed in 11 (21.1%) cases during treatment with ethionamide; however, thyroid stimulating hormone levels came back to normal after discontinuation of the drug. One of these cases developed myxoedema coma, and died in the hospital. Seven (13.4%) patients developed arthralgias (with elevated serum uric acid levels of 8.3 and 9.1mg/dl respectively) attributed to pyrazinamide, which responded to non-steroidal anti-inflammatory drugs in most of the cases.

Among the study group 8 (15.3%) cases (previously published) had XDR-TB according to the prescribed definition (Bikram *et al* 2008) .Only one among these is still alive, smear and culture negative, and under regular follow-up. Overall among the 52 cases of MDR-TB, 37 patients (77.1%) were successfully cured, 11 (21.1%) cases died, and 4 (7.6%) patients who defaulted during the second year of treatment were lost during follow-up.

DISCUSSION

The emergence of MDR-TB is a global problem, which is threatening to destabilize the best efforts of TB control (WHO/HTM/TB/2006, Dhingra *et al* 2008, Behera 2007 &Nathanson 2004), and has been attributed to factors such as non-adherence to treatment, inappropriate treatment regimens, drug malabsorption, poor drug quality, and a poor health infrastructure for effective delivery of treatment (Behera 2007, Nathanson 2004 & Drobniewski 2002). To manage MDR-TB in poor economically settings, the WHO and its partners launched the DOTS Plus initiative to develop a global policy to provide technical assistance to DOTS programmes and to enable access to second-line drugs under rational use (WHO/HTM/TB/2006, (Nathanson 2004,Drobniewski 2002,Chaudhury and Thatte 2003). The present study demonstrated that 5.7% of TB patients had MDR-TB with initial and secondary resistance in 36.5% and 63.4% of those, respectively. These figures are almost consistent with the recently published reports from various other parts of India (Behera 2007, Mondal and Jain 2007). The tabulated figures quoted by Sharma and Mohan (Table 3) (Sharma and Mohan 2004) also demonstrate the magnitude of MDR-TB identified in previous studies.

However, the exact incidence/percentage of MDR-TB isolates was not mentioned in two recent (2007-2008) hospital-based Indian studies involving 66 and 27 cases of MDR-TB, respectively (Arova *et al* 2007 &Dhingra *et al* 2008) .

Similar to previous studies, the majority of our cases were males (Yew *et al* 2000, Telzak *et al* 1995). A statistically significant ($p < 0.001$) cure rate of 77% was seen in our patients, which is definitely more than that observed in the most recent (2008) published reports of Dhingra and co-workers (Dhingra *et al* 2008) from New Delhi, and, more consistent with the figures of 60% to 96% observed in New York, Turkey, South Korea, Peru and Hong Kong (Dhingra *et al* 2008, (Telzak *et al* 1995,Tahaoglu et al 2001,Lambregts *et al* 1998, Perri and Bonora 2004 & Mitnick *et al* 2003). Fortunately, most of the patients in our study were able to afford the cost of investigations and drug therapy, and a portion below the poverty line was provided financial assistance by various existing non-governmental organizations.

Globally, MDR-TB has been a particular concern among HIV-infected persons, whose rate of survival is substantially lower than that of those not infected (Arova *et al* 2007, Perri and Bonora 2004, (Pereira *et al* 2005, Sharma *et al* 2005 & Sungkanuparph *et al* 2007), and testing for HIV is recommended for all TB patients (WHO/HTM/TB/2006).Only one XDR-TB case in our study was co-infected with HIV and this patient died at home (Bikram *et al* 2008). The WHO recommended treatment for MDR-TB is the same for HIV-infected and non-HIV-infected patients except for the use of thioacetazone, which should not be used in HIV-infected cases, (WHO/HTM/TB/2006).

Worldwide, the prevalence of MDR-TB and XDR-TB is one the rise. Per the published reports of 2008, the frightening emergence of XDR-TB has been reported globally in 45 countries, with the highest prevalence of 19% observed in Latvia (Raviglione 2008 ,Udwadia 2008 &WHO/HTM/TB/2008).Among our study group, eight patients (15.3%) were found to have XDR-TB, only one of whom was successfully saved while as the remaining seven (13.4%) died (Bikram *et al* 2008). The adverse effects of drug therapy in our patients were mostly minor (e.g., nausea, vomiting, hypersensitivity reactions), as observed in previous studies (Dhingra *et al* 2008, Behera 2007 & Nathanson *et al* 2004),and were managed with symptomatic treatment. Major side effects included hepatitis, psychosis, and ethionamide-related hypothyroidism, which were meticulously treated. More intense TB-control programmes should be instituted for rapid diagnosis and aggressive treatment for favorable outcomes. Treatment delivery to patients, which may be carried out using effective hospital- and community-based approaches, can be accomplished even in resource-poor settings. Besides DOTS-Plus programmes, aid for socioeconomic problems and the provision of emotional support to patients and their families are necessary for adherence to therapy and overall cure. Finally, future studies involving large samples are needed to learn more about the resistance pattern and outcome of both MDR-TB and XDR-TB.

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