ORIGINAL ARTICLE

Prevalence and drug resistance pattern of MDR TB in retreatment cases of Punjab, Pakistan

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Abstract

Objective: To determine the prevalence and resistance pattern of multidrug-resistant tuberculosis.

Methods: This cross-sectional study was carried out from January 2010 to June 2014 in nine tertiary care hospitals implementing programmatic management of drug-resistant tuberculosis in Punjab, and comprised retreatment tuberculosis cases. Data was collected from the Electronic Nominal Review System. SPSS 17 was used for data analysis.

Results: Of the 1,250 cases, 861(69%) were of multidrug-resistant tuberculosis confirmed through drug sensitivity testing. The mean age was 32 (±13.5 SD) years. Besides, 664(53%) were males and 1,208(97%) resided in urban areas of Punjab. Multidrug-resistant tuberculosis was found to be more prevalent in the most productive age group, i.e. 15-45 years, with 709(57%) cases ($p<0.05$), in urban areas1, 208(97%) cases ($p<0.05$) and in the pulmonary site 852(68%) cases ($p<0.05$). Overall, 391(41%) cases showed resistance to all first-line anti-tuberculosis drugs while 239(28%) showed resistance to oral first-line drugs. Besides, 526(42%) cases showed resistance to fluoroquinolones and 650(52%) to second-line drugs. Of them, 420(81%), ($p<0.05$) patients showed highly significant resistance to fluoroquinolones and 26(5%) to ethionamide.

Conclusion: There is a need to fully implement national tuberculosis guidelines with a focus on expansion and effective implementation of directly observed therapy short course in order to prevent further emergence of drug resistance.

Keywords: Multi Drug Resistance, Retreatment Cases, Prevalence, ENRS, PMDT. (JPMA 66: 989; 2016)

Introduction

The magnitude of tuberculosis (TB) is increasing globally. It has great impact on the cause of death and illness, especially in Asia. It is one of the most common infectious diseases in Pakistan. The world's sixth-most populous country is ranked fifth among 22 high-burden TB countries. In 2012, an estimated 8.6 million people developed TB. The World Health Organisation (WHO) estimated incidence and prevalence rates of TB in Pakistan at 231 and 376 cases per 100,000 people, respectively, in 2012.[1] Now, multidrug-resistant tuberculosis (MDR-TB) has become an emerging health issue with great challenges for public health sector in Pakistan. According to the WHO, MDR retreatment cases among the notified pulmonary TB cases were 3,700(880-6,600) and laboratory-confirmed MDR retreatment cases were 55 out of 1,602 in 2012 in Pakistan.[2] Around 56% of the country's TB cases are detected in Punjab, the most populous province. Of them, 75% fall in productive age group, i.e. 15-45 years. The prevalence of TB patients in Pakistan is 376/100,000.[1,2]

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The number of MDR-TB patients in Pakistan is difficult to estimate as drug sensitivity testing on internationally-accepted protocols has recently started in the country.[3] However a Little or no data exists on the prevalence and/or drug resistance pattern amongst high-risk MDR-TB groups in the province. Studies have shown that certain factors enhance the risk of acquiring MDR-TB, including lack of knowledge about the disease, not giving adequate consideration to TB patients, long waiting time, poor economical condition, non-compliance due to certain reasons, specifically side effect of anti-Tuberculosis treatment (ATT) and prolonged treatment.[4] Migration, gender, age and previous TB treatment history are also associated with the increased risk of MDR-TB. TB patients who had failed first-line anti-TB treatment, defaulted during the treatment and had relapsed after the treatment are at high risk of MDR-TB.[4,5]

First-line drugs (FLDs) to cure TB such as streptomycin, ethambutol and pyrazinamide showed high co-resistance patterns from the drug susceptibility test.[6] MDR-TB cases are more difficult to treat because there is long duration of treatment, i.e. at least 18-24 months with second-line drugs (SLDs), including fluoroquinolones (FQs). These anti-TB drugs are more expensive, more toxic and less cogent than the FLDs. The high rate of mortality and

prevalence of TB in poor sections of the country may be higher because these patients have limited access to hospital medical services. The current study was planned to determine the prevalence and drug resistance patterns of MDR-TB in retreatment cases in Punjab.

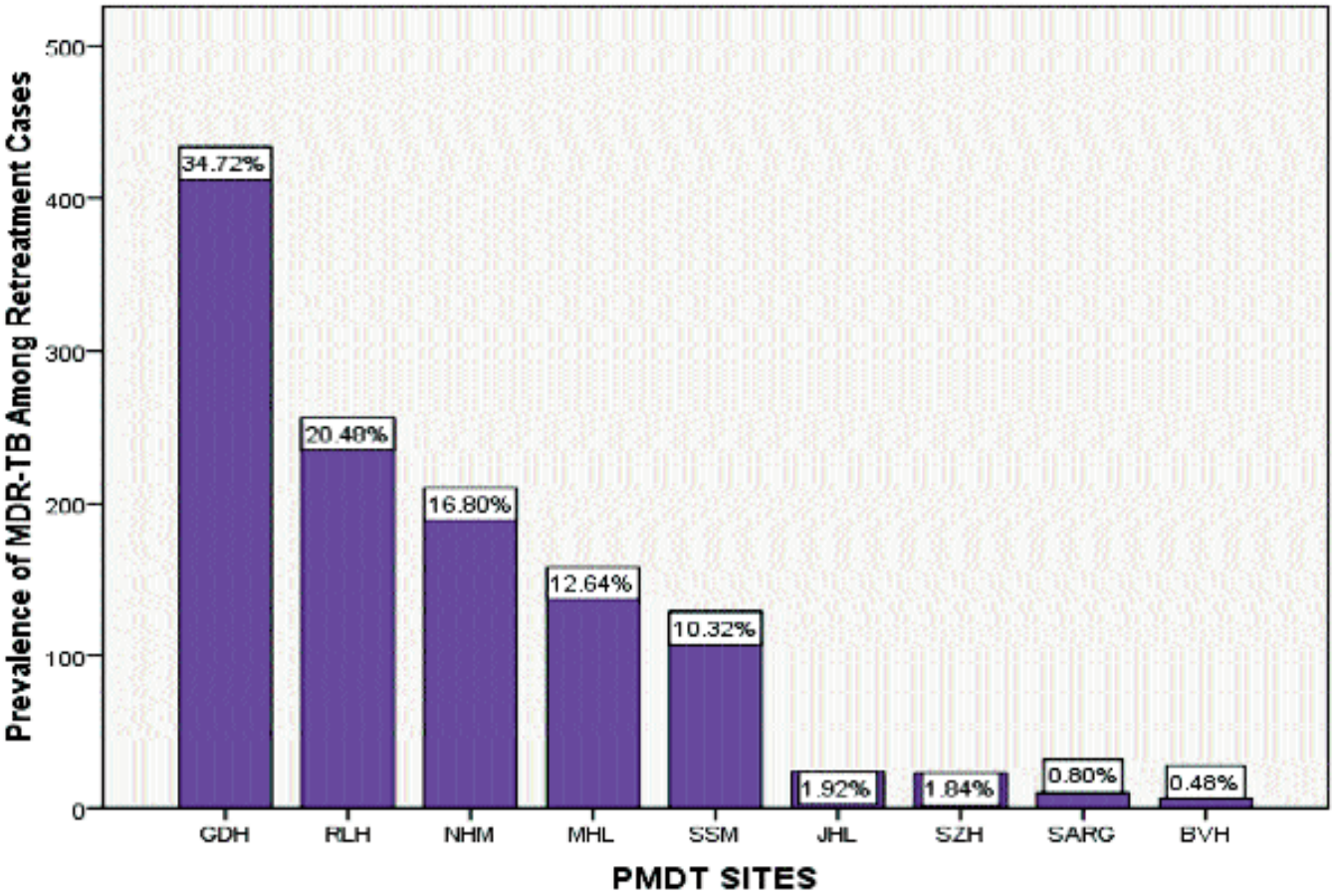
Patients and Methods

This cross-sectional multi-site study was carried out from January 2010 to June 2014 in nine tertiary care hospitals implementing Programmatic Management of Drug-Resistant TB (PMDT) in Punjab, Pakistan. Retreatment cases were further classified by their most recent course of treatment outcome: such as 'relapse', 'treatment after failure', 'lost to follow-up' and 'other'. All retreatment cases later diagnosed as MDR-TB cases and registered at PMDT sites were included. Patients with a record of previous treatment for less than 30 days or no anti-TB drug history were excluded. Medical records of the patients were assessed in terms of patient demographic characteristics and drug-resistance pattern. Demographic parameters included age, gender, region, occupation and behaviour status. Clinical parameters were drug-susceptibility testing (DST) and culture test.

Using non-probability convenience sampling, medical records were accessed from the Electronic Nominal Review System, an electronic system that keeps record of MDR patients all over the country. Microsoft Excel 2007 was used to capture and code the medical records of patients with DST and culture-confirmed MDR-TB. SPSS 17 was used for statistical analysis. For descriptive statistics the continuous variables were summarised using mean and categorical variables were summarised in terms of percent in each category.

Results

Of the 1,423 retreatment cases identified, 1,250(88%) were included. Of them, 158(12.64%) cases were from



MDR-TB: Multi-drug-resistant tuberculosis. PMDT: Programmatic management of drug-resistant tuberculosis.
GDH: Gulab Devi Hospital, Lahore. RLH: Rawalpindi Leprosy Hospital. NHM: Nishtar Hospital, Multan. MHL: Mayo Hospital, Lahore. SSM: Samli Sanatorium Murree. JHL: Jinnah Hospital, Lahore. SZH: Sheikh Zayed Hospital, Rahim Yar Khan. SARG: District Headquarter Hospital, Sargodha. BVH: Bahawalpur Victoria Hospital.

Figure: Prevalence of MDR-TB in Retreatment Cases in Different PMDT Sites of Punjab.

Table-1: Distribution of Retreatment Cases in Punjab.

Groups	MDR (Resistance to Rifampicin (R) and Isoniazid (H) with or without any other drug)	Mono or Poly resistance other than MDR	Total
Retreatment	861(69%)	389(31%)	1250
◆ Relapse	141	75	216
◆ Default	48	29	77
◆ Treatment after failure	574	225	799
◆ Other+	98	60	158

MDR: Multidrug resistance.

Table-2: Resistance Pattern of First Line Drugs (FLD) and Second Line Drugs (SLD) in Retreatment Cases.

Resistance to FLD including S	Relapse n (%)	Default n (%)	Failure n (%)	Others n (%)
H	02 (1.41)	00 (0.00)	01 (0.17)	01 (1.02)
HR	04 (2.84)	00 (0.00)	17 (2.96)	06 (6.12)
HRZ	11 (7.80)	02 (4.17)	20 (3.48)	05 (5.10)
HEZ	01 (0.71)	00 (0.00)	05 (0.87)	00 (0.00)
HRE	02 (1.41)	02 (4.17)	14 (2.44)	03 (3.06)
HRS	07 (4.96)	04 (8.33)	21 (3.66)	02 (2.04)
RES	00 (0.00)	00 (0.00)	01 (0.17)	00 (0.00)
HRES	15 (10.6)	05 (10.4)	54 (9.41)	17 (17.3)
HREZ	23 (16.3)	24 (50.0)	162 (28.2)	30 (30.6)
HRZS	09 (6.38)	04 (8.33)	31 (5.40)	06 (6.12)
HEZS	00 (0.00)	00 (0.00)	01 (0.17)	00 (0.00)
HREZS	67 (47.5)	07 (14.6)	247 (43.0)	28 (28.6)
Resistance to SLD				
Fluoroquinolones (FQs)	83(58.9)	36 (75.0))	335 (58.4)	72 (73.5)
ETO	4 (2.84)	2 (4.17)	18 (3.14)	0 (0.00)
FQ,ETO	2 (1.41)	5 (10.4)	13 (2.26)	5 (5.10)
FQ,KM	1 (0.71)	2 (4.17)	5 (0.87)	3 (3.06)

MDR: Multidrug resistance
Isoniazid (H), Rifampicin (R), Ethambutol (E), Pyrazinamide (Z), Streptomycin (S), Ethionamide (ETO), Kanamycin (KM).

Table-3: Demographic Characteristics of MDR-TB in Retreatment Cases.

Characters	Retreatment Cases MDR (Resistance to Rifampicin (R) and Isoniazid (H) with or without any other drug (n= 861)	Mono or Poly resistance other than MDR (n= 389)	Total (n= 1250)	P value
Gender				
Male	462	202	664	0.57
Female	399	187	586	
Age				
0-14	14	17	31	
15-45	709	287	996	0.000
≥ 46	138	85	223	
Region of Origin				
Rural	35	7	42	0.04
Urban	826	382	1208	
Occupation				
Employed	395	160	555	0.118
Unemployed	466	229	695	
Drug Addiction				
Yes	13	9	22	0.317
No	848	380	1228	
Behaviour Status				
Smoker	57	10	67	0.003
Non smoker	804	379	1183	
Site of TB				
Pulmonary	852	379	1231	0.041
Extra pulmonary	9	10	19	
Previous TB Treatment History Status				
Relapse	141	75	216	
Default	48	29	77	0.023
Treatment after failure	574	225	799	
Others	98	60	158	

MDR: Multidrug resistance
TB: Tuberculosis.

Mayo Hospital Lahore (MHL), 434(34.72%) Gulab Devi Hospital (GDH), Lahore, 210(16.8%) Nishtar Hospital Multan (NHM), 256(20.48%) Rawalpindi Leprosy Hospital (RLH), 129(10.32%) Samli Sanatorium Muree (SSM), 24(1.92%) Jinnah Hospital Lahore (JHL), 10(0.8%) district headquarter hospital (DHQ) Sargodha (SARG), 23(1.84%) Sheikh Zayed Hospital (SZH) Rahim Yaar Khan and 6(0.48%) Bahwalpur Victoria Hospital (BVH) (Figure). Of all the cases, 664(53%) were males and 695(56%) were unemployed. The mean age with standard deviation was 32±13.5 years (range 10-86 years)

Moreover, 574(46%) cases were treatment failures, 141(11.28%) relapsed, 48(3.84%) defaulted and 98(7.84%) cases did not provide sufficient information, though they had had first line drugs (FLD) resistance records. Of the retreatment cases, 59(5%) new cases, 108(9%) with unknown previous treatment history and 6(0.4%) with missing information were excluded. Besides, 861(69%) were MDR-TB cases confirmed through DST, while the remainder showed resistance to one or two drugs other

than isoniazid (H) and rifampicin (R) combined (Table-1).

The prevalence of any drug resistance among the retreatment cases significantly increased during the study period (January 2010 to June 2014) from 98(7.8%) to 638(51%) while the prevalence of MDR-TB retreatment cases increased from 113(9%) in 2010 to 550(44%) in 2013($p<0.05$). The prevalence of MDR-TB among the failure cases [574(67%), ($p<0.05$)] was higher compared to relapse 141(16%), default 48(6%) and other cases (11%). Besdies, 349(41%) retreatment MDR-TB cases showed resistance to all FLDs with streptomycin (S) while 239(28%) showed resistance to oral FLDs (RHZE) (Table-2). Resistance to rifampin (R) and isoniazid (H) with or without any other drug (861(69%), $p<0.05$) was significantly more common in the retreatment cases compared to mono or poly resistance other than MDR. Of the 526(42%) retreatment cases resistant to FQs, 26(5%) showed resistance to ethionamide (Eto) and 11(2%) to kanamycin, amikacin and capreomycin. Around 420(81%) ($p<0.05$) MDR-TB patients showed highly significant resistance to FQs.

Finally, 22(2%) patients said yes to 'drug addiction' and 1208(97%) resided in urban areas of Punjab (Table-3). MDR-TB was more prevalent in the most productive age group 15-45 years (709(57%); $p<0.05$), in the urban areas of Punjab (1,208(97%); $p<0.05$) and in the pulmonary site (852(68%); $p<0.05$).

Discussion

In a study by Wahab et al. drug resistance and MDR-TB was found significant in category II patients ($p=0.03$, $p=0.0001$, respectively).[4] The study ascertained a high prevalence of MDR-TB amongst the retreatment cases. The mortality rate among the MDR-TB patients is approximately 60%.[7] Another Pakistani study demonstrated previous history of FLDs is the most common risk for developing the MDR-TB.[8] A study from India has shown that the resistance to any of the FLDs i.e. 46.9% to isoniazid, 27.6% to rifampicin, 33.7% to ethambutol and 34.7% to streptomycin in retreatment cases.[9] National TB Control Programme guidelines recommended Streptomycin along with four FLDs for the treatment of retreatment TB patients.[10] Out of 1,250 MDR-TB retreatment cases, 41% of retreatment cases showed resistance to all FLDs with streptomycin (RHZES) while 28% showed resistance to oral FLDs (RHZE).

In retreatment DST-confirmed MDR cases the prevalence of the resistance to all FLDs including streptomycin was observed up to 44% ($p=0.000$). This study showed high resistance to all FLDs with streptomycin but, in contrast with a few other Pakistani studies, reporting low resistance as 1.8% for primary MDR-TB.[11] A study published by Javed et al. in 2008 showed an overall increasing trend of resistance to all FLDs ($p=0.001$).[12] The prevalence of MDR-TB among the treatment failure cases (67%, 0.023) was higher as compared to relapse (16%), default (6%) and other cases (1%). The high proportion of MDR-TB cases with treatment failure posesa challenge to the efficacy of the retreatment regimen. As compared to another study, treatment failure category among the retreatment cases using SLDs were at high risk of MDR-TB ($p=0.02$) and there was a trend towards poor outcome among them (42.9%, $p=0.13$).[3] In contrast with another Pakistani study, 55.6% MDR-TB patients were lost to follow-up and defaulted and 5.6% patients were facing the treatment failure status.[13]

In the present study, a majority of the MDR-TB patients were from a lower economic background (54%), although poverty was not statistically significant for the occurrence of MDR-TB ($p=0.118$). Similarly, addiction has no statistical impact on the prevalence of MDR-TB ($p=0.570$). There were 462 male cases of MDR-TB found in the study with an overall prevalence of 54% and MDR-TB resistance had statistically great impact on the productive age ($p=0.000$). Many studies from all over the world indicated male gender and pulmonary TB as risk factors of the MDR-TB. Another study observed that young males, poverty and previously-treated TB patients are significantly associated with pulmonary MDR-TB.[14] Another study indicated that MDR-TB was significantly associated with previous TB treatment ($p=0.001$), male ($p=0.002$), age under 45 years ($p=0.01$), poor living conditions ($p=0.002$) and unemployment ($p=0.01$).[15]

The study, however, has its limitations. The sample size was small and the resistance pattern was only measured among those patients who were registered at PMDT sites and were enrolled on SLDs.

Conclusion

The prevalence of MDR-TB among retreatment cases was alarmingly high. Drug-resistant TB, including MDR-TB, has been a serious public health problem in Pakistan and will greatly affect TB control strategies. There is a need to fully utilise the National TB guidelines with a focus on expansion and effective implementation of directly-observed therapy short course (DOTS) in order to prevent further emergence of drug resistance. The findings of the study support the recommendation to find the high rate of primary drug resistance and need to develop a strategy for those patients who have dropped out of their treatment protocol to control the MDR-TB.

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