Original Article

Multidrug Resistant Tuberculosis in Punjab, Pakistan

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ABSTRACT

Background: Tuberculosis (TB) can be traced back to the beginning of the mankind. It is a bacterial infectious communicable disease. Globally, TB is the second major cause of death from infectious diseases. MDR-TB is a type of tuberculosis that is resistance to at least two first line anti-tuberculosis drugs Isoniazid (INH) and Rifampicin (RMP) with or without resistance to other drugs. Multidrug resistant TB (MDR-TB) caught attention, when it emerged in the USA in 1990. Globally 425,000 new cases emerge annually, which is almost 5% of the annual global TB burden. Pakistan is included in 27 high burden MDR-TB countries, with almost 2% to 3.2% for newly diagnosed and 35% for previously treated patients. The overall aim of this study was to assess the burden and the distribution of resistance for four anti-tuberculosis medications. **Method:** A cross sectional study design was used. Data was collected from the hospital records of microbiology department, for the patients between the duration of January 2008 to December 2011. Forms of 300 patients were collected and analyzed. Epi-data and SPSS software were used for analysis. An outcome variable was developed and analysed. Correlation of resistance was analysed with different independent variables such as age, sex, residence (rural/urban), duration of disease, TB treatment history, smear reports and sensitivity results. **Results:** The results of this study showed the variation of resistance to four different drugs, but most resistance was found for rifampicin and lowest for Ethambutol. The resistance was found Isoniazid (49%), Streptomycin (52%), Rifampicin (68%), and Ethambutol (25%). Resistance between male/female and rural/urban was not prominently different. Among the different TB types, MDR-TB patients were found to be more resistant, with the highest resistance for Rifampicin (80%) and the lowest resistance for Ethambutol (31%). The extent of the lesion had no association with the resistance prevalence. Age was significantly associated with resistance. Previous ZN smear negative reported cases appeared to be more resistant. **Conclusion:** This study suggests for improvements in the early detection and treatment. Old test techniques such as ZN smear should also be replaced by more reliable and efficient laboratory techniques. There is also a need to improve the record keeping system in order to have complete information about the diseases and patients.

INTRODUCTION

Tuberculosis (TB) can be traced back to the beginning of the mankind[1]. It is a bacterial infectious communicable disease caused by Mycobacterium tuberculosis, which mostly affects the lungs. Globally, TB is the second major cause of death from infectious diseases. It is a major cause of morbidity and mortality in developing countries[2]. Even after immense efforts by scientists, drug resistant tuberculosis especially multidrug-resistant tuberculosis (MDR-TB) constitutes a considerable challenge to control TB. The emergence of MDR-TB and XDR-TB is indication of that challenge and has become a grave public health concern in many countries.[3]

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Multidrug resistant TB (MDR-TB) caught attention, when it emerged in the USA in 1990.[4] MDR-TB is a type of tuberculosis that is resistance to at least two first line anti-tuberculosis drugs Isoniazid (INH) and Rifampicin (RMP) with or without resistant to other drugs. Globally 425,000 new cases emerge annually, which is almost 5% of the annual global TB burden.[5] According to a WHO survey in 2008, globally the incident cases of MDR-TB were 440,000 with 150,000 deaths[6,7] of the 440,000 cases in WHO Regions, the distribution was 69,000 were in Africa, 8,200 in America, 24,000 in Eastern Mediterranean, 81,000 in Europe,[8] 130,000 in South-East Asia and 120,000 in Western Pacific region.[9] In the African region, the magnitude of MDR-TB among TB patients is generally low, with the frequency range of 0.5% to 3.9% among new TB cases and 0.0% to 16.7% among previously treated TB patients. Almost 50% of MDR-TB cases worldwide are estimated to occur in China and India. China is a country with high burden of disease. Globally, about 22% of MDR-TB burden is found in China. According to the world health organization report of 2008, the emerging cases of MDR-TB were estimated to be 99,000 in India.[10]

Pakistan has a population of over 160 million. According to a study conducted from January 2007 to April 2010 at Holy Family Hospital, Rawalpindi, Pakistan is included in 27 high burden MDR-TB countries, with almost 2% to 3.2% for newly diagnosed and 35% of previously treated patients.[11] Recently, Pakistan has been ranked as the fourth highest MDR-TB burden country and fifth highest TB burden country in the world.[12] Patients often do not comply with the prescribed treatment regimen because of lengthy treatment, poor economic condition, low education status, inadequate social support mechanisms and side effects of medications. This is causing an emergence of drug resistant tuberculosis that presents threat to the global health community. Another major reason for this resistance is that people choose not comply with the complete course of treatment or sometimes do not have access to medicines to complete the course. Also a lesser proportion of MDR-TB are cured as compared to drug-susceptible TB.[13]

The National Tuberculosis Program (NTP) is faced by different challenges related to health systems, the community, interventions and implementation.[14] The first survey about tuberculosis was conducted in 1962. In 1993 the directly observed treatment short-course (DOTS) strategy was approved by the government of Pakistan. Recently, each province was given responsibility to plan and manage its own NTP under federal NTP guidelines. Two major objectives were defined: (1) to increase the cure rates up to 85% for positive cases, and (2) to increase the detection of new cases up to 70% after getting first objective.[15]

Rationale

The rationale for this study was to highlight the burden, the pattern and the distribution of disease in order to convince the policy maker of the necessity to conduct research on larger- scale and in a comprehensive way.

Aim

The overall aim of this study was to assess the burden and the distribution of resistance for four anti-tuberculosis medications.

MATERIALS AND METHODS

Study design and setting

Exposure and outcome were taken at the same time. It was like a snapshot of population at single point in time to assess the disease prevalence, so cross sectional study based on hospital record was done. This study design was supported by some other studies.[11, 16, 17] Data was collected from Gulab Davi Chest Hospital, one of the oldest hospitals in the city of Lahore, a city with population exceeding ten million. The hospital treats more than 80% of the tuberculosis patients. An average of 600 patients visits the out-patients department (OPD) every day.[18]

Data collection and sampling

The author visited the hospital himself to collect the data from hospital records of the Microbiology Department of Gulab Davi Chest Hospital Lahore, Pakistan. The data was found in the form of culture sensitivity reports and collected in March 2012. Each report was comprised of close ended questions. A tool was developed by the author according to the required variables for study. These reports included information about

demographics (age, sex, and address), duration of disease, extent of lesion, medication compliance, TB treatment history, previous ZN smear reports and sensitivity results. . The forms were collected from January 2008 to December 2011. Although the institute constituted a big tertiary health care hospital, the number of recorded cases did not reflect the total number of cases, because of poor hospital recordkeeping.

Definitions of variables

Radiological extent of lesion: It describes the extent of disease or inflammation. Radiology (CXR) is used in the diagnosis and measurement of tuberculosis extent. There are three categories of extent in this study, which are unilateral, bilateral and clear extent.

Previous treatment: Patients who were taking anti-TB treatment in the past. The patients were categorized into three classes: irregular treated patients, regular treated patients and not treated patients.

Previous ZN smear report: Ziehl-Neelsen (ZN) staining technique as a choice for the smear microscopy to detect the tuberculosis mycobacteria in the sample. This variable contains information about the report of ZN smear test done in the past.

ZN smear report: This smear report is the current one at the time of culture sensitivity test.

Tuberculosis types: In this study, four categories were made on the basis of the type of tuberculosis. These types were categorized as follows: pulmonary TB, MDR-TB, extra-pulmonary TB and Unknown TB.

Suspected and Non-suspected cases: Patients coming in the hospital were assessed by the physician to be suspected or not-suspected for the drug resistance before referring to microbiology department for culture sensitivity tests.

Statistical analysis

A data file was created by the author himself. First, data was entered into EpiData software and then transferred to Microsoft excel and IBM SPSS Statistics 20. The independent variables were selected according to available information in the culture sensitivity reports. A dichotomous outcome variable was formulated and analyzed. . In the outcome variable all individuals included, who were resistant to either two or more than two drugs, labeled as outcome positive.

RESULTS

Data from all four years 2008 to 2011 was analyzed. The total number of study participants was 300. There were 131 cases in 2008, 68 cases in 2009, 36 in 2010 and 65 in 2011. The mean age was 36.30 with the range from 3 to 90 years. Out of total 300, 176 were males and 122 females. The numbers of participants in urban and rural settings were 156 and 104 respectively.

Resistance to Isoniazid

Resistance to Isoniazid was 48% among males and 50 % among females. Among participants from urban and rural areas resistance was 49 % and 53 % respectively. Fifty percent of the regularly treated patients included in this study were resistant. Resistance among patients with bilateral extent of lesion on X-ray was 52% compared to those with unilateral extent of lesion who had 43% resistance. Of the 172 positive participants 53 % were resistant and 60 % were resistant among the 10 participants with negative ZN smear. Only five patients were not taking isoniazid before and have a resistance of 25%.

Resistance to Streptomycin

For Streptomycin there was too much missing data. There were only 69 participants out of a total of 300. Among males, 61 % were resistant and for females 40 % were resistant. For rural patients resistance was 49 % while for urban patients, it was 57 %. For new and already treated cases there were similar percentages of resistance. The resistance among previously ZN smear positives was 51 % with no resistance in negative reported cases. The resistance among patients taking or not taking Streptomycin was similar, i.e., 59 % and 54 % respectively.

Resistance to Rifampicin

Resistance to Rifampicin was highest among all four drugs. It was similar among males and females at 68 %. Resistance among rural residents was 67 % compared to 69 % among urban. A high resistance of 96 % was found among those who had a history of taking regular treatment compared to 68 % receiving irregular treatment and 63 % of those not treated at all. The resistance among previously ZN smear positives was 73 % with

48 % in negatively reported participants. The resistance in patients taking Rifampicin previously, was 71 %.

Resistance to Ethambutol

Resistance to Ethambutol was the lowest among all four drugs. The resistance to Ethambutol among males was 26 % and 23% among females. In contrast to Rifampicin, sensitivity to Ethambutol in residents from both urban and rural areas was higher. Resistance was 24% among both rural and urban residents. Resistance among patients who were not treated before was 15 % compared to 27 % who were regularly treated and 23 % who were irregularly treated. The patients with previously positive ZN smear report were 33 % resistant and for negatively reported patients resistance was 12%. The participants who were not taking Ethambutol before were 100 % sensitive while those who were previously taking Ethambutol were 29 % resistant.

Multidrug resistant TB (Univariate analysis)

Univariate analysis was performed on outcome variable to determine the association of anti-tuberculosis drug resistance with clinical and demographic characteristics of participants. Few associations of statistically significant results were obtained.

As shown in Table 2, MDR-TB was found to significantly increase with age (OR=1.0, 95%CI 1.00-1.03). Previously ZN smear report negative (OR=2.9, 95% CI 1.29-6.93) was associated with resistance. Resistance to two or more than two drugs among previously negative ZN smear reported patients was 3 times higher than previously positive reported cases.

Table 1: Frequencies of resistance for independent variables: (A) Isoniazid, (B) Streptomycin, (C) Rifampicin, (D) Ethambutol

(A) Isoniazid

Variables		Sensitive	Resistant	Total	Resistance Risk Ratio
Gender	Male	86	80	166	0.48
	Female	57	57	114	0.5
	Total	143	137	280	0.49
Residence	Rural	47	52	99	0.53
	Urban	74	70	144	0.49
	Total	121	122	243	0.50
Previous Treatment	No Treated	17	13	30	0.43
	Regular	69	70	139	0.50
	Irregular	24	19	43	0.44
X-Ray[1]	Unilateral	25	19	44	0.43
	Bilateral	103	111	214	0.52
	Clear	3	2	5	0.4
Previous ZN Smear	positive	80	92	172	0.53
	Negative	4	6	10	0.6
TB Types	Pulmonary	37	52	89	0.58
	MDR	14	21	35	0.6
	Extra pulmonary	13	5	18	0.28
	Unknown	78	59	137	0.43
History of Isoniazid	Positive	100	107	207	0.52
	Negative	3	1	4	0.25

[1] X-ray examination: shows TB lesions and extent of spread of the disease in the lungs.

(B) Streptomycin

Variables		Sensitive	Resistant	Total	Resistance Risk Ratio
Gender	Male	15	24	39	0.61
	Female	18	12	30	0.4
	Total	33	36	69	0.52
Residence	Rural	15	14	29	0.49
	Urban	13	17	30	0.57
	Total	28	31	59	0.52
Previous Treatment	No Treated	3	4	7	0.57
	Regular	14	17	31	0.55
	Irregular	7	8	15	0.53
X-Ray[1]	Unilateral	7	9	16	0.56
	Bilateral	24	24	48	0.5
	Clear				
Previous ZN Smear[2]	positive	22	23	45	0.51
	Negative	2	No	2	0
TB Types	Pulmonary	11	6	17	0.35
	MDR	2	5	7	0.71
	Extra pulmonary	No	1	1	1
	Unknown	20	24	44	0.55
History of Isoniazid	Positive	9	13	22	0.59
	Negative	12	14	26	0.54

(C) **Rifampicin**

Variables		Sensitive	Resistant	Total	Resistance Risk Ratio
Gender	Male	54	116	170	0.68
	Female	37	77	114	0.68
	Total	91	193	284	0.68
Residence	Rural	32	64	96	0.67
	Urban	46	104	150	0.69
	Total	78	168	246	0.68
Previous Treatment	No Treated	11	19	30	0.63
	Regular	44	98	142	0.96
	Irregular	14	30	44	0.68
X-Ray	Unilateral	15	30	45	0.67
	Bilateral	69	149	218	0.68
	Clear	1	4	5	0.80
Previous ZN Smear	positive	48	127	175	0.73
	Negative	14	13	27	0.48
TB Types	Pulmonary	25	67	92	0.73
	MDR	8	33	41	0.80
	Extra pulmonary	5	11	16	0.69
	Unknown	52	82	134	0.61
History of Isoniazid	Positive	61	149	210	0.71
	Negative	2	4	6	0,67

(D) **Ethambutol**

Variables		Sensitive	Resistant	Total	Resistance Risk Ratio
Gender	Male	113	40	153	0.26
	Female	90	27	117	0.23
	Total	203	67	270	0.25
Residence	Rural	68	24	98	0.24
	Urban	110	35	145	0.24
	Total	178	59	243	0.24
Previous Treatment	No Treated	22	4	26	0.15
	Regular	101	37	138	0.27
	Irregular	31	9	40	0.23
X-Ray	Unilateral	33	13	46	0.28
	Bilateral	162	53	215	0.25
	Clear	4	No	4	0
Previous ZN Smear	positive	111	54	165	0.33
	Negative	23	3	26	0.12
TB Types	Pulmonary	67	21	88	0.24
	MDR	27	12	39	0.31
	Extra pulmonary	10	5	15	0.33
	Unknown	97	30	127	0.24
History of Isoniazid	Positive	142	57	199	0.29
	Negative	6	No	6	0

[2] Previous ZN smear: ZN smear done in the past. ZN smear is a staining technique detecting the TB mycobacteria in the sample.
[3] MDR: Drug resistance of two or more any anti-TB drugs (according to data record available in hospital)

Table 2: Univariate Logistic Regression

Variable		OR	LCI	UCI
Age In years		1,0	1,00	1,03
Sex	Male	1		
	Female	0,8	0,53	1,35
Residence	Rural	1		
	Urban	1,2	0,70	1,89
Radiological extent of lesion	Unilateral			
	Bilateral	0,9	0,49	1,73
	Clear	0,7	0,49	1,73
Illness duration (in years)	-	0,9	0,98	1,01
Previous treatment	No treated	1		
	Regular	0,9	0,44	2,05
	Irregular	1,2	0,49	3,05
INH taken	yes	1		
	No	1,8	0,29	10,77
RM taken	Yes	1		
	No	2,4	0,43	13,24
Duration of RM taken (in months)	-	0,9	0,94	1,04
ETH taken	Yes	1		
	No	2,4	0,43	13,24
Duration of ETH taken (in months)	-	0,986	0,94	1,04
STP taken	Yes	1		
	No	1,0	0,59	1,81
Duration of STP taken (in months)	-	1,1	0,98	1,27
Drug resistance	Suspected	1		
	Not suspected	2,8	0,81	9,55
Previous ZN smear report	Positive	1		
	Negative	2,9	1,29	6,93
ZN smear report	Positive	1		
	Negative	2,3	0,99	5,59
Sensitivity test	Not done	1		
	Done	0,9	0,06	15,09

DISCUSSION

The results of this study showed the variation of resistance to four different drugs, the highest resistance was found for Rifampicin and lowest for Ethambutol. There was no prominent difference in resistance among gender and between rural and urban residents for three of the medicines. The patients, who had been taking medications regularly in the past (but did not complete the whole course of treatment), were found to have more resistance. No association between the extent of lesion and resistance was found. Age and previously negative ZN smear reported cases had significant association with outcome variable.

Some prior published studies reported mixed results of the resistance to anti-tuberculosis drugs. In this study resistance to RMP, SM, INH and EMB was observed, being 68 %, 52 %, 50 % and 25 % respectively. Resistance to Rifampicin was highest, while in another study Rifampicin was considered as a substantial predictor of resistance to Isoniazid and Streptomycin.[19] For Ethambutol, the resistance was the lowest. Another study done by Khurram et al, reported the lowest resistance for Ethambutol, but the overall resistance was found higher in MDR-TB strains.[11] Among rural and urban residents, the resistance was not found prominently different for these drugs except for the 1st line anti-TB injectable drug Streptomycin. Rural residents were slightly less resistant for Streptomycin. As this injectable drug is not easily available in rural areas unlikely to other first line medications that are available due to TB control program. Due to limited use of second line medications among rural resident, they are less resistant.

As expected, the previous history of treatment has been found to be the strongest predictor of drug resistance or MDR-TB in previous studies. In this study the resistance to each medicine was slightly higher in the patients, who have been taking medicine regularly in the past (did not complete the whole course of TB treatment in the past and not taking medicine now), while persons who were not taking medicine had low resistance, which shows most probably the mutation of bacteria is a contributing factor. Mdivani's study found that the prevalence of MDR-TB in newly diagnosed patients (10.5 %) and of retreatment cases (53.1 %) and retreatment was found to be the strongest predictor of resistance.[19] Many other studies have also recognized previous treatment as an established risk factor for drug resistance.[20,21] The reasons for more resistance may include the mutation of bacteria, the exposure to resistant strain of TB, immunodeficiency, HIV and poor compliance etc. In univariate analysis, resistance was slightly higher in patients using medicine irregularly. With regard to previous treatment, noncompliance is a significant challenge to overcome the worst situation of MDR-TB in the country. Compliance can be affected by many factors. One of them is long duration of treatment caused to circumvent the TB treatment, gauge to development of M/XDR-TB strain.[22] Another factor may be encountered side effects. A Chinese study reported that 12.6 % of TB patients face the problem of side effects during treatment.[23] Other factors may include lengthy and expensive treatment, stress and early relief.

The extent of lesion (on x-ray) was not found to be an associated factor for the resistance to the anti-TB drugs either, which shows that some other factors may be responsible such as, late diagnosis and treatment commencement, poor compliance, exposure to resistant strain etc.

Tuberculosis can affect any race, gender and age. There are mixed results in different studies about resistance distribution in gender and age. In this study there was no considerable difference of resistance between males and females, in contrast to other studies reporting higher resistance in male isolates.[24,25,26,27] While two other studies, one from Pakistan[28] and other from Georgia[19] reported that females were at higher risk of MDR-TB. This contradiction may relate to different social and cultural norms.

Age had a significant association with outcome variable. Each year 1.3 % resistance was increased, so elderly were found having high resistance. This result was in agreement with the Mdivani's study, that found more resistance in age groups 25-34 and 35-44 years than 15-24 years,[19] but in contrast to this, Ejaz's study found higher MDR-TB cases under the age of 28 years,[28] while some other studies reported low resistance in young children as well as in elderly.[26, 27]

Surprisingly, the patients who were suspected to be drug resistant by their physician had lower resistance than the patients who were not suspected for drug resistance, which indicates a gap in health care system and medical doctors training. Many TB trainings are frequently conducted in the country but drug-resistant TB training is deficient. Medical doctors are not always well trained and often lack awareness of the problem especially in rural areas, which may cause delay in detection, diagnosis and treatment inception. Local practitioners should be targeted in the training programs, because they are closer to communities and their services are available at affordable rates and many patients go to them.

This study found high resistance among patients who were reported negative in previous ZN smear test in the past, which highlights the situation of morbidity in society and more people are getting resistant strain of TB. A Pakistani study reported increased trend of resistance over a period of 17.5 years.[27]

The study showed very high resistance for all drugs. Several factors might have contributed for increased resistance. The hospital has no system to assign a specific number to patients. The record is saved in paper form and not in electronic form in the computer. Resistant patients normally return to the hospital frequently, and chances for duplication are quite high leading to overrepresentation in the study sample. The hospital does not have proper infection control system and nosocomial infection is also a contributing factor for other patients during their hospitalization or consultation, to get resistant strain of TB. HIV patients are more at risk because of low immunity. Patients from small cities or periphery come to this big hospital in worst condition of resistance, causing high representation of resistant cases. Other factors for increased resistance may include the improperly formulated or adulterated and spurious medications, non-continuous medicine chain supply and inadequate administration of medicine to the patients.

CONCLUSION

In conclusion the burden of MDR-TB is very high in the country and increasing overtime. This study found variations in resistance for different anti-TB drugs. The burden of MDR-TB is similar in male/female and rural/urban. The gap was found in the health care system and medical doctors trainings. It is strongly recommended for the improvement in the diagnostic tools and techniques for MDR-TB detection and training of medical doctors and general practitioners

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