PREVALENCE OF RESISTANCE TO 1ST LINE ANTI TUBERCULOSIS DRUGS AT RAHIM YAR KHAN

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ABSTRACT

Background: Tuberculosis is an important infectious health issue and its control strongly rely upon effective treatment. The drug resistance and its pattern are important determinant of the treatment regimen, its duration and outcome. **Objective:** To determine the frequency and pattern of drug resistance among 1st line anti tuberculosis treatment. **Methodology:** It was a cross sectional study carried on 100 cases of smear positive TB. This study was conducted from 1st January 2010 to 30 June 2011. Detailed demographic data and history of ATT was taken and their sputa were sent for drug susceptibility testing on LJ media. The cases with drug resistance and no previous history of ATT were labeled as primary while those with previous history of ATT were labeled as secondary resistant cases. The data was entered and analyzed by using SPSS version 15. **Results:** Out of 100 patients enrolled, drug susceptibility report was available for 87 isolates as sputum failed to grow any organism in 13 patients. Out of these 87 cases, 48 (55.17%) were males and 39 (44.83%) females with age range of 9-91 years. Seventeen out of 87 patients (19.5%) had previous history of ATT. Out of 87 isolate, 62 (71.26%) were sensitive to all 1st line drugs (R, H, E, Z, S) while 25 (28.74%) were resistant to one or more drugs. Primary resistance was seen in 17 (24%) out of 70 cases in contrast to secondary in 8 (47%) out 17. The difference between primary and secondary resistance among various drugs was statistically significant for isoniazid (p value 0.003*)* and pyrazinamide (p value 0.036) while the difference to streptomycin, ethambutol and rifampicin was insignificant with *p* values of 0.20, 0.35 and 0.09 respectively. There was no case of primary MDR-TB and 5.9% of secondary MDR-TB. None of the sociodemographic parameter was significantly associated with drug resistance. **Conclusion:** Resistance to 1st line anti-tuberculosis drugs at Rahim Yar Khan is still common. There are good number of patients in which this resistance pattern compromise the currently recommended regimens. However, larger surveillance studies are needed to strengthen this evidence.

Key words: 1st line ATT, Drug resistance, MDR-TB, Tuberculosis.

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INTRODUCTION

Drugs Resistant tuberculosis (TB) remained the biggest threat to control of the disease.[1] A combination of effective 1st line anti-tuberculosis drugs i.e. Rifampicin (R), Isoniazid (H), Pyrazinamide (Z), Ethambutol (E) and Streptomycin (S) not only ensure cure of an individual patient but also stop spread of disease in the community. Emergence of drug resistance is influenced by a number of factors like poor prescribing practices of treating doctors, noncompliance of patients, poor quality, non-availability and adverse effects of drugs etc.[1-3] In a particular society, presence of such adverse factors will determine the frequency and severity of drug resistance to anti-tuberculosis drugs. As these factors differ from country to country and even in different localities of same country so should be the pattern of resistance to these drugs.[4,5] This fact is quite evident in the 4 reports published by the Global Project on Anti-Tuberculosis Drug Resistance Surveillance since 1994.[6-9] According to 4th global anti-tuberculosis drug resistance report by WHO, resistance to at least one anti tuberculosis drug ranged from 0% in Iceland to 56.3% in Baku, Azerbaijan. The proportion of MDR ranged from 0% in eight countries to 19.4% in the Republic of Moldova and 22.3% in Baku, Azerbaijan. A retrospective review of data from Cape Town, South Africa presented at the IUATLD World Conference on Lung Health. 8-12 November 2007 showed that overall 5.6% of 17, 615 MDR isolates collected from 2004 to 2007 were XDR-TB, however, the figures differed across various provinces with KwaZulu-Natal reporting as high as 14% of MDR cases as XDR-TB.[9]

In developed world, drugs susceptibility testing (DST) is done on all isolates of Mycobacterial TB responsible for human disease and treatment is guided by these DST results.[10,11] However, in developing world where disease is more prevalent, such costly and time consuming practices are not feasible due to lack of financial resources. Therefore,

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TB is empirically treated and DST is reserved only for drug resistance suspects.[12] Majority of studies on drugs resistance are reported from tertiary care centers,[4,13,14] which usually cater difficult to treat cases from wide drainage area or published from Mycobacterial reference labs[15,16] which obviously receive samples from patients suspected to have drug resistant TB. Therefore, the results of such studies might not reflect the true magnitude of drug resistance in the community.

Department of Pulmonology, Sheikh Zayed Medical College / Hospital, Rahim Yar Khan enjoys a special position as it serves as a primary centre for diagnosis and treatment of tuberculosis patients of Rahim Yar Khan City and surrounding villages under DOTS TB control program. Additionally it is a tertiary care referral centre for the whole district of Rahim Yar Khan as well as the districts of Rajanpur, D.G Khan and adjoining areas of Sindh & Baluchistan. We decided to conduct a surveillance study to determine the magnitude of resistance to 1st line anti-tuberculosis drugs on cases of Pulmonary TB from the area covered by Sheikh Zayed Medical College / Hospital, Rahim Yar Khan, treatment and diagnostic centre under DOTS.

METHODOLOGY

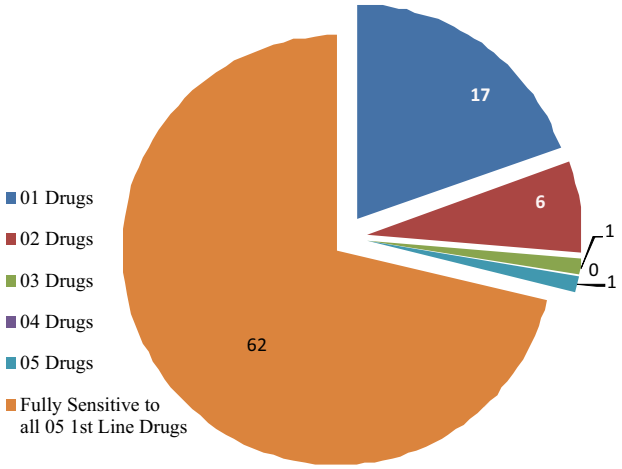
This cross sectional study included one hundred consecutive sputum smear positive Pulmonary Tuberculosis (PTB) patients of either age & sex irrespective of previous history of ATT from the DOTS catchment area of Sheikh Zayed Medical College/Hospital, Rahim Yar Khan. Extra Pulmonary TB and smear negative Pulmonary TB cases were excluded. Patients belonging to areas other than the DOTS catchment area, were also excluded. This study was conducted from 1st January 2010 to 30th June 2011.

An informed consent was taken from all eligible patients to be included in this study. Sociodemographic (age, sex, educational status, residence etc), as well as disease related data like previous history of ATT was recorded on prescribed performa. All subjects of study were properly instructed to bring early morning sputum in a sterilized sputum container. Samples were processed and cultured on solid Lowenstein Jensen (LJ) medium for a minimum of 6 weeks, Mycobacterial isolates were then tested for their susceptibility to 1st line anti tuberculosis drugs. The concentration of drug used per ml of LJ medium for susceptibility testing was 02 mcg for streptomycin, 0.2 mcg for isoniazid, 05 mcg for ethambutol, 01 mcg for rifampicin and 100 mcg for pyrazinamide. The results were entered analyzed on SPSS version 15.0.

RESULTS

Out of 100 patients enrolled, drug susceptibility report was available for 87 isolates. In 13 patients, sputum failed to grow any organism (AFB culture Negative). Out of total 87 evaluable subjects, 62 were sensitive to all 1st line drugs (R, H, E, Z, S) while 25 isolates were resistant to one or more drugs. (Figure I).

Figure I: Overall sensitivity (susceptibility) to one or more 1st line anti tuberculosis drugs



Seventeen out of 87 patients (19.5%) had previous history of anti-tuberculosis treatment while 70 out of 87 had no previous history of anti-tuberculosis treatment. Table I shows the relation of previous history of anti-tuberculosis drugs to presence of drug resistance to one or more drugs.

Table-II shows the overall resistance to individual 1st line ATT drugs as well as resistance in those with (secondary resistance) or without anti-tuberculosis treatment (Primary resistance). Resistance to all 1st line drugs was more common in patients with previous history of anti-tuberculosis treatment. However, the difference was statistically significant for isoniazid (*p value 0.003*) and pyrazinamide (*p value 0.036)* however, it was not significant in case of streptomycin, ethambutol and rifampicin.

Table I: Presence of drug resistance to one or more drugs versus history of anti tuberculosis treatment

Resistance		Secondary Resistant H/O ATT n=17	Primary Resistant NO H/O ATT n=70	Total n=87
Resistant to One or More Drugs		**08 (47.1%)**	**17 (24.3%)**	**25 (28.7%)**
Resistant to one drug	17	03	14	
Resistant to 02 drugs	06	03	03	
Resistant to 03 drugs	01	01	00	
Resistant to 04 drugs	00	00	00	
Resistant to 05 drugs	01	01	00	
Fully Sensitive t o all 05 1st Line Drugs		**09 (52.9%)**	**53 (75.7%)**	**62 (71.3%)**

Table II: Resistance to individual drugs in relation to history of anti tuberculosis treatment

Drugs	Secondary Resistance H/O ATT n=17	Primary Resistance No H/O ATT n=70	Overall Resistant Total n=87	P Value
Streptomycin	5 (29.4%)	12 (17.1%)	17(19.05%)	**0.20**
Pyrazinamide	2 (11.8%)	0 (00.0%)	2 (02.3%)	**0.03**
Isoniazid	7 (41.2%)	6 (8.6%)	13 (14.9%)	**0.003**
Rifampicin	1 (5.9%)	1 (1.4%)	2 (2.3%)	**0.35**
Ethambutol	2 (11.8%)	1 (1.4%)	3 (3.4%)	**0.09**
MDR	01 (5.9%)	00 (00.0%)	01 (1.0%)	-----

Table III: Sociodemographic characteristics of participants of the study

Variables	Total Patients 87	Resistant 25	Fully Sensitive 62	P Value
AGE (Years)				
Range	9-91	10-75	9-91	---
Median	32.00	33.00	30.00	---
Mean	34.64	37.24	33.60	--
SEX				
Male	48	14	34	**0.55**
Female	39	11	28	
RESIDENCE				
Urban	67	19	48	**0.54**
Rural	20	06	14	
EDUCATION				
Uneducated	44	16	28	**0.08**
Educated	43	09	34	
MARITAL STATUS				
Never Married	28	06	22	**0.21**
Married	59	19	40	
Approximate in Rupees				
Less Than 15000	78	23	55	**0.49**
More Than 15000	09	02	07	

Multi drug resistance (MDR) (resistance to at least rifampicin and isoniazid with or without resistance to other anti-tuberculosis drugs) was found in one patient with previous history of anti-tuberculosis treatment. Sociodemographic characteristics of participants of this study are shown in table III. The table also compared these factors between the patients having fully sensitive MTB and those having resistance to one or more drugs. Difference was not statistically significant, with any of the sociodemographic parameters.

DISCUSSION

This study has revealed that resistance is highest for streptomycin (19.05%) followed by Isoniazid (14.9%), Ethambutol (3.4%), Pyrazinamide (2.3%) & Rifampicin (2.3%). Although the figures may differ but most of other studies also revealed that resistance was highest to Streptomycin followed by isoniazid regardless of history of treatment.[17] Both of these (S & H) are the oldest drugs available to treat TB (1947 & 1951) respectively. Both have been used in era when split therapy was used, this can partially explain higher resistance to both these drugs. However if consider the case of streptomycin, presently it is used for retreatment cases and shorter period of duration, its resistance should have been down. Possible reason for this high resistance might be its cross resistance with other aminoglycosides, especially amikacin, gentamicin and kanamycin which are extensively used to treat other non-tuberculous conditions. One of the reasons of higher resistance to INH might be the quality of drug. Due to its very low price, it has never been a priority of pharmaceutical companies to manufacture INH alone, in era when split therapy was used. It was left to local companies with poor quality control to manufacture & market it. This might have an impact on higher resistance to INH. One the other hand, Rifampicin, Ethambutol and Pyrazinamide are introduced later at a time when recommendations of fixed dose combinations were implemented, efficacy of these drugs is still protected.

Streptomycin is considered for retreatment cases as 5th drug in current recommendations,[18] but in this study 05 out of 17 patients (29.4%) who had been previously exposed to anti tuberculosis treatment were resistant to these drugs. (Table II) Adding of one drug to this group in which 1 out of every 3 patients is expected to be resistant needs further debate and justification.

As streptomycin is not recommended for treatment

of new cases, we excluded streptomycin from analysis, to see the resistance pattern of other four drugs i.e. RHEZ. Seventy two out of 87 isolates (82.8%) were fully sensitive to all four drugs i.e. (RHEZ). 12 isolated were resistant to any one drug. Two were resistant to any two & only one was resistant to all four drugs. Considering this data, current recommendations of using four drugs (RHEZ) in intensive phase for all cases may be quite adequate to treat 84 out of 87 (96.6%) patients where 03 drugs will be available during the intensive phase. In another two patients, two drugs will be effective in intensive phase & in remaining one case of this study, which is MDR case none of the drug is effective. But during the continuation phase, where use of two drugs R & H are recommended currently, one patient of this study was left with no effective drug & another 12 were left with rifampicin only & one with INH only. Therefore 14 out of 87 patients (16.1%) were left with an inadequate regimen. So, if Ethambutol is added in continuation phase, the regimen may be effective & adequate in 96.6% of patients of this study.

WHO has estimated that 4.8% (95% Cl 4.6-6.0) of all TB cases are resistant to one or more drugs. The highest burden (50%) present in china and India and about 7% of these drug resistant cases are found in Russian Federation. Pakistan is the fourth highest among high-burden drug-resistant-TB countries. Globally, an estimated 3.3% of new TB cases and 20% of previously treated cases have MDR-TB, a level that has changed little in recent years. It is estimated that there are 24.475 (95% CI 15737 – 73132) MDR TB cases in eastern Mediterranean region. Pakistan contributes almost 60% of this burden. According to WHO estimates, overall incidence of MDR TB is 0.5% (95% CI 1.6-9.4), in new cases is 3.4% (95% CI 0.5-18) and in retreatment cases 36.5 % (95% CI 8.7-75.3). However in this study one out of 17 had MDR TB while none of the 70 new cases had it. This gives a combined proportion of MDR TB of 1.2%, 0.0% of primary MDR-TB and 5.9% of secondary MDR-TB. All these figures are lower than the WHO estimates as well as various other studies reported from other parts of Pakistan.[19-23]

Table V shows an interesting comparison of overall resistance to various anti Tuberculosis drugs in various studies in which the main author (Masood-ul-Haq) was involved. PMRC study,[15] included all specimen sent to PMRC Mycobacterial laboratory on the suspicion of drug resistance. Mayo hospital study,[13] included all patients admitted at a tertiary care center; obviously these patients had disease severe enough to be cared as indoor patient. On the other hand, in this study, all diagnosed patients of smear positive Pulmonary TB whether admitted or treated as outpatient from catchment area of DOTS diagnostics and treatment center of Sheikh Zayed Hospital, Rahim Yar Khan were included. Different inclusion criteria might be one explanation for higher resistance in PMRC study and Lahore study as compared to this study. (Table V)

Table V: Comparison of overall resistance to various anti Tuberculosis drugs; Impact of different inclusion criteria

Drugs	PMRC Lahore (Pakistan) Study[15]	Mayo Hospital Lahore (Pakistan) Study[13]	Current Study (SZMC/HRYK)*
Isoniazid (H)	25.43%	25%	14.9%
Rifampicin (R)	25.00%	15%	2.3%
Ethambutol (E)	10.00%	12%	3.4%
Pyrazinamide (Z)	21.49%	Not done	2.3%
Streptomycin (S)	24.12%	19%	19.1%
MDR (R+H)	10%	11%	1.0%

Another reason for a lower level of Rifampicin resistance and MDR in our study might be due to effective implementation of DOTS program. It is generally considered that with effective treatment of TB cases, the resistance to drugs is likely to go down while non-compliance with TB control guidelines will result in higher incidence of drug resistance. At our center right from start, TB control program is always headed by a TB and Chest specialist and dedicated staff cared to register the patients, educate them and maintain the record. Services were further improved as it became the tertiary care center and post graduate training started. However it has to be proved with further drug resistance surveillance studies involving the other centers in our district and other districts involving larger number of patients.

There are few limitations to this study. Firstly, small number of patients included because of lack of funds needed to do the drug susceptibility tests. Secondly, smear negative TB and extra pulmonary TB cases were excluded. Both of these groups are considered pauci-bacillary TB (Fewer number of MTB) while smear positive PTB is likely to higher bacillary burden and therefore higher chances of resistance. Therefore, it is possible that if all TB cases are included, (Smear Positive and Smear negative as well as extra pulmonary TB cases), resistance pattern

might be different. Therefore it is recommended that studies involving larger number of patients and all types of TB should be considered for more accurate picture of drug resistance.

As the drug resistance pattern is likely to be changed depending upon the effectiveness of TB control measures, periodic surveillance studies at local and national levels should also be done.

Conclusion: Our study showed that while following the current recommendations of using two drugs (R and H) in about 16% of cases of TB patients will be left with only one drug either R or H which is inadequate. It warrants addition of a third drug in continuation phase. So further studies with larger number of patients and analysis of available data may be recommended to validate this finding and recommend any change in current practices.

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