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Resistance Patterns among Multidrug-Resistant Tuberculosis Patients: A Multi-Center Study from Pakistan

Rabab Batool[1], Muhammad Imran[2*], Abdul Hafeez Kandhro[3], Zainab Barry[4], Naseem Salahuddin[4] & Muhammad K H Uddin[5]

[1]The Aga Khan University Hospital, Karachi, Pakistan.
[2]The College of Medical Technology, Zia Uddin Medical University, Karachi, Pakistan.
[3]Healthcare Molecular and Diagnostic Laboratory Hyderabad, Pakistan.
[4]The Indus Hospital, Karachi, Pakistan.
[5]The Department of Material Sciences and Engineering, Kroto Research Institute, The University of Sheffield, United Kingdom.
***Corresponding Author Email ID:** imranmuhammad@zu.edu.pk
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Abstract

Background: The high burden of multi-drug resistance tuberculosis (MDR TB) is a matter of great concern. The increasing resistance to anti tuberculosis drugs has been the area of growing concern and are posing threats to TB control. The aim of this study was to evaluate the drug resistance patterns for the first line and second line anti-Tuberculosis drugs in multiple drug resistant tuberculosis (MDR-TB) patients.

Method: The study was retrospective, observational, employing purposive, non-random sampling technique for data collection conducted at the TB Clinic- of the different healthcare centers in the provinces of Pakistan Sindh and Baluchistan from December 2010 to May 2016. All bacteriologically confirmed TB patients who were found to be Rifampin Resistant (RR) on Genotypic drug susceptibility testing (GXP), or detected to be drug resistant on phenotypic Universal drug susceptibility testing were enrolled into the study.

Results: Out of total 3776 patients, 96.3% were resistant to Rifampicin and 94.7% were resistant to Isoniazid. 25.5% isolates were resistant to all five first line drugs. Resistances against Pyrazinamide and Ethambutol was 54.2% and 51.6% respectively. 36.3% patients were resistant to Fluoroquinolones (FQ), 9.7% were resistant to Ethionamide (Eto) and 4.1% were resistant to both FQ and Eto. 33.5% patients were MDR plus resistant to FQ. However, the resistance to both FQ plus Aminogycosides was quite low, 2.7%.

Conclusion: The drug resistance rates are quiet high in MDR-TB for both first line and second line drugs. The standardized MDR TB regimen needs to be updated, based on the prevalence of drug resistance patterns in the community for the effective management of drug resistant TB.

Keywords

Multiple drug resistant tuberculosis, Resistance, Genotypic drug susceptibility testing, Phenotypic Universal drug susceptibility testing, Aminoglycosides.

Introduction

Drug resistance pattern among MDR-TB patients is of critical importance for its role in designing of individualized regimen and the control of TB[1, 2]. Pakistan ranks five among the 22 high burden countries in the world for MDR TB[3, 4].The results of a recent drug resistance surveillance carried out in Pakistan by the National TB Control Program (NTP), estimated MDR TB in

newly notified TB cases as 3.7%, and in previously treated cases for TB as 18.1%[5]. Resistance to the drugs develops due to an inadequate regimen, poor quality drugs and interrupted treatment with anti TB drugs.

MDR TB treatment is widely available in Pakistan through the programs implemented by the National TB Control Program (NTP) and supported by Global Fund5. WHO protocol for case finding strategy is followed strictly. GeneXpert (GXP) test and TB culture with Drug Sensitivity Testing (DST) are performed on all re-treatment cases, DR TB contacts, new under -treatment pulmonary TB patients who remain smear positive till the end of intensive phase, presumptive MDR, people living with human immunodeficiency virus (HIV), children under the age of five years, and all samples taken through procedures (bronchoalveolar lavage, CSF, biopsy) [5].

All patients diagnosed on GXP and show resistance to rifampicin are put on standardized second line drugs (SLDs) recommended by WHO [5]. All contacts with TB are presumed to have the same DST as the index case and are started on the same regimen, until DST results become available in 4-6 weeks. The regimen may be modified as needed, based on the DST results.

The primary aim of this study was to document the resistance patterns of the MDR TB patients for the first line and second line drugs in Pakistan.

Methodology

The study was retrospective, observational, employing purposive, non-random sampling technique for data collection. All bacteriologically confirmed TB patients who were found to be RR on Genotypic drug susceptibility testing (GXP), or detected to be drug resistant on phenotypic Universal DST from December 2008 to May 2016 were enrolled in the Healthcare Centre's situated in provinces of Sindh and Baluchistan, Data was extracted from Electronic Numerical Recording System (ENRS) that is a uniform format for data storage provided by NTP across all Programmatic management of drug resistant tuberculosis (PMDT) sites. The collected data was then analyzed using Spss version 19.0. Frequency distribution and percentages were calculated using frequencies.

Results

During the study period December 2010 till May 2016, 3776 patients were enrolled on ENRS of all 9 PMDT sites. 1812 (48%) were male, with the mean age 35 years (range 1-85 years). DST results were available for 2985 (79%) patients and were included in the study, while GXP test was performed for 3144 (83.3%) patients. The results of Universal DST were not always mutually exclusive with GXP results, as discrepancies were often noted: RR might be detected on GXP, but susceptible to Rifampicin on Universal DST; RR might not be detected on GXP but phenotypic result may show RR on DST. Patients detected as RR on GXP, while culture reported negative at baseline were 278 (7.4%) as given in table 1; cases that were RR on GXP, and resistant on DST to drugs other than Rifampicin were 68 (2%), while 25 (0.7%) cases had no RR reported on GXP, while the culture DST represented RR. Eight (0.3%) patients were treated under the program, based on their clinical presentation or contact history.

Table 1: Reasons for enrollment into MDR TB Treatment.

ALL SITES (N=3776)	**N**	**%**
Available DST results	2985	79.1
Available GXP results	3144	83.3
Only GXP Rif Res + Culture Negative	278	7.4
Rif Res on GXP + with DST results (R>H) to complement MDR	68	1.8
Suspects/Contacts treated (No bacteriological evidence of MDR TB)	8	0.3
No Rif Res on GXP/enrolled on DST	25	0.7

DST= drug susceptibility testing, GXP=Gene Xpert,
Rif Res=Rifampicin Resistant, R>H=Resistant to Isonaizid,
MDR TB=Multiple drug resistant tuberculosis

The overall resistance pattern for the first and second line ATT are shown in Table 1. While table 2 shows resistance to all first line drugs was seen in 775 (25%) of the cases. Resistance to at least rifampicin and isoniazid was seen in 2760 (93%) of the patients , while the rest were enrolled on MDR regimen as they were RR on GXP, or RR with resistance to drugs other than isoniazid on DST. A significant number of patients, i.e. 1085 (36%) had fluoroquinolone (FQ) resistance. Moreover, resistance to ethionamide (Eto) was also significant among this cohort 291 (10%). Hence, the probability of co resistance with isonaizid in patients found to be RR on Gene Xpert is 93%. Co-resistance of Eto with FQ was 4%. The prevalence of extensive drug resistance (XDR) TB (defined as resistance to isoniazid and rifampicin plus any FQ and at least one second-line anti-TB injectable drug) was 3%. 3111 (83%) of the patients were diagnosed on GXP results and enrolled on standardized regimen till their DST results became available.

Table 2: Drug Resistance Patterns identified through phenotypic Universal Drug Sensitivity Testing (n=2985)

H	**2827**	**94.7%**
R	2874	96.3%
E	1540	51.6%
Z	1619	54.2%
HR	2760	92.5%
HRE	1525	51.1%

HRZ	1591	53.3%
HRS	1403	47.0%
HREZ	1129	37.8%
RHZS	877	29.4%
SHREZ	755	25.3%
AM	66	2.2%
Cm	42	1.4%
Ofx	1085	36.3%
Eto	291	9.7%
MDR+Ofx	1000	33.5%
Ofx/Mfx+Am/Km/Cm	81	2.7%
Ofx+Eto	122	4.1%

H=Isonaizid, R=Rifampicicn, E=Ethambutol, Z=Pyrazinamide, S=Streptomycin, Am=Amikacin,Cm=Capreomycin, Ofx=Ofloxacin, Eto=Ethionamide, MDR=Multiple Drug Resistant, Km=Kanamycin

Discussion

A number of studies have been conducted to find the resistance patterns of first line and second line drugs. Several studies have already been done in Pakistan but the limitation was smaller sample size and not representative of a large population[2, 3].This is the first multi-center study representing the prevalence of resistance to first line and second line TB drugs in Pakistan. One such study was done by Rao, N. A., et al at Ojha Institute of Chest Diseases (OICD) Karachi[2], but the sample of 577 patients taken from patients enrolled only at OICD, which is a tertiary care hospital and hence, the sample was not representative of a large population. In our study the MDR plus FQ resistance was 34%, which was 7% higher than the study conducted at OICD While the same study reported 56.5%, resistance against all five first line drugs this study shows 25%. Resistance to pyrazinamide and ethambutol was reported as 76.6% and 73% respectively, as compared to this study that shows 51.6 % and 54.2% respectively[2]. Rao et al., reported resistance to FQ and Eto as 7.3 % and 1.8% respectively, which is significantly lower than the results found in this study, i.e. 36.3% and 9.7%[2].

Another study conducted at Armed forces institute of pathology (AFIP) Rawalpindi, Pakistan reported resistance to the FQ and all first group five drugs 52.7% and 62.6% respectively[3], which is higher than that found in our study, i.e. 25% and 36%. The same study showed resistance to Eto as 13% while in our cohort it was found to be 9%. The study however had smaller sample size (100 patients) and a single center study[3].

Another study conducted in Mumbai, India reported resistance to fluoroquinolones as 69.1%[6], which is much higher than that found in our study. The same study reported resistance with amikacin and capreomycin as 14% and 12%, which is much higher than that found in our study (2% and 1% respectively). Discordance was also found in resistance to Eto (50% versus 9% in this study). The prevalence of presumed XDR and XDR TB (resistant to isoniazid and rifampicin plus any FQ or at least one second-line anti-TB injectable drug) reported in Mumbai was 4.1% and 56.8% respectively while in our study it was 2.7% and 37%[6]. Other studies from Pakistan have also reported high resistance from first line and second line anti-tuberculosis drugs in MDR TB patients[7, 8] and declare it an

alarming situation and emphasize special attention to the patients for better treatment outcomes because resistance to anti-TB drugs increases the risks for poor treatment outcomes[9].

Conclusion

The standardized MDR TB regimen needs to be updated, based on the prevalence of drug resistance patterns in the community for the effective management of drug resistant TB, and to prevent the transmission of infection in the community. Primary and acquired resistance patterns of the population may help to select the regimen for new and re-treatment cases.

Conflicts of Interests

None.

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