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Drug Resistance Patterns among XDR-TB Patients visiting a TB Centre at a Tertiary Health Care Facility

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Abstract

Background: Resistance to MDR TB has additional resistance to fluoroquinolones and second line injectables it is defined as XDR-TB. The present study is designed to evaluate drug resistance patterns in such XDR patients. Aims and Objectives: To study drug resistance patterns in XDR-TB patients. **Material and Methods**: Researcher carried out a cross-sectional study over a period of two years. In this study, 43 patients were studied. The criteria used to observe was that – Newly diagnosed cases of XDR-TB patients by using the second line Drug Sensitivity Testing (DST). This method was used at an accredited RNTCP lab regardless of age and gender of the patients. Further, demographic, clinical and treatment data were analyzed in terms of drug sensitivity of the patients. **Results**: 48.83% of patients showed resistance with fluoroquinolone, 20.93% showed resistance with XDR with Second line injectables, 30.23% with flouroquinolones + second line injectibles. Maximum resistance was seen in Ofloxacin (81.4%) followed by kanamycin (44.2%). 41.86% patients were diabetics showing that drug resistance was more prevalent in these population. Maximum defaulters (80%) were from the lower class. **Conclusion**: Flouroquinolones and second-line drugs must be administered rationally and considerately to prevent the widespread drug resistance. The role played by diabetes and lower socio economic status in the emergence of drug resistance must not be undermined.

Keywords: Diabetes, Drug Sensitivity, Fluoroquinolones, XDR TB, MDR TB

1. Introduction

Definition – Extensively Drug-Resistant (XDR) is defined as a rare type of multidrug resistant tuberculosis. It is resistant to isoniazid and rifampin along with any type of fluroquinolone. It is also resistant to minimum of one of the three injectable second line drugs such as amikacin, or capreomycin.

"A MDR TB patient whose biological specimen is additionally resistant to atleast a FQ (Ofx, LfxMfx) and a second line Ianti-TB drug (Km, Am, Cm)."

Since last 5000 years tuberculosis has affected one third of global population and is being affecting 5000 new cases daily and causing loss of two lives every three minutes worldwide[1]. In India, 'infectious smear positive TB cases' alone accounts for 0.8 million out of

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1.9 million new cases diagnosed every year. According to WHO report India accounts for 28 deaths per 1,00,000 population due to TB and leads in the list of highest death rate among all communicable diseases. Of all avoidable adult deaths due to communicable diseases, 24% is due tuberculosis alone.[2]

Studies conducted in India previously found newly detected tuberculosis cases later diagnosed as MDR-TB accounted to 3% while the retreatment cases accounted to 17.2%. Field study done in Gujarat by Ramachandran et al concluded 3.2% of cases of XDR strains from MDR cases[3–5]. Although the data shows relatively a smaller number of cases of MDR-TB but the threat to healthy population of India due to rising number of XDR-TB cases are worrisome.

In developing countries where the burden of tuberculosis is rampant the outbreak of newer TB strains and large cases of XDR-TB may increase due to non-compliance of antibiotic guidelines and irrational use of second line drugs.

The DOTS plus program which was launched with the motto to diagnose and treat MDR-TB cases has been threatened by the emergence of XDR-TB strains.

XDR-TB is defined as Mycobacterium Tuberculosis resistant to isoniazid, rifampicin, one of the fluoroquinolones and any one of three injectable drugs, i.e., kanamycin, amikacin and capreomycin[6,7]. Pre-XDR-TB is defined as strain that is resistant to either Flouroquinolones or second line injectibles[16]. Study found there was no prevalence of XDR strains in Antarctica whereas they were found in rest of the globe[8]. Although there is poor data to find prevalence of XDR-TB cases in India, the drug sensitivity reports of second line drugs of anti-tuberculosis indicate 5%-15% of MDR-TB cases later developed XDR-TB.

The RNTCP certified laboratory attached to our centre has been performing DST for first line ATT drugs for last 10 years and second line ATT drugs for last three years. Therefore, we conducted this study in order to find out the drug resistance pattern in XDR-TB patients.

Justification of conducting this study – The study was done to know the exact percentage of resistance to second line injectables and combined resistance of both at our DRTB centre which caters the population from districts viz. Nashik, Dhule, Nandurbar, Jalgaon. This study was conducted in order to identify and assess the patterns of drug resistance in XDR-TB patients. Through this study, the researcher aimed at analyzing the different ways in which the XDR-TB patients resist to drugs. Findings of this study can be used by future scholars and experts of the field to determine ways through which such resistance can be reduced and better drugs can be developed by the relevant authorities.

2. Aims and Objectives

To Study Drug Resistance Patterns in XDR-TB patient.

3. Materials and Methods

The present study was a retrospective as well as prospective observational study conducted in the Drug Resistance TB Centre of the Department of Respiratory Medicine of a Tertiary care health Institute. The study was conducted over a period of 2 years from August 2016 to September 2018. 43 patients fulfilling the eligibility criteria were studied over this duration. Minimum sample size was calculated using this formula:

$$\frac{Z^2 p^* q L^2}{}$$

Where Z = 1.96 (critical value)

p = proportion of the diseased P = 0.06

q = 1-p

L = margin of error = 5%

3.1 Eligibility Criteria

3.1.1 Inclusion Criteria

- Newly diagnosed cases of XDR-TB patient using second line Drug Sensitivity Testing (DST). Method done at accredited RNTCP lab irrespective of age and sex.
- Patients giving informed written consent.

3.1.2 Exclusion Criteria

- Patients not willing to give informed consent

3.2 Methodology

The study was conducted in the Department of Respiratory Medicine and DR-TB centre located at MVPS Dr Vasantrao Pawar Medical College, Nashik which includes four districts.

43 patients were attending the Department of Respiratory Medicine and DR-TB centre located at MVPS Dr Vasantrao Pawar Medical College, Nashik were randomly included in the study, after satisfying the eligibility criteria and approval from the ethics committee with ethical clearance. The study was conducted for a period of 2 years from August 2016 to September 2018.

The patients were classified depending on their socio-economic strata according to modified Prasad's classification.

Patient selection was done randomly irrespective of age group, sex or any comorbidities that satisfied the inclusion criteria.

Cases of XDR-TB were diagnosed by using second line Drug Sensitivity Test (DST) method by at Intermediate Reference Laboratory (IRL) located at Pune and Nagpur.

Written informed consent was taken from all study participants and only those who gave consent were enrolled.

The detailed clinical history and demographic profile of the patients was evaluated and analyzed with respect to drug sensitivity of the patients.

3.3 Statistical Analysis

All the collected data was entered in Microsoft Excel sheet and then transferred to SPSS software ver.17 for analysis. Qualitative data was presented as frequency and percentages and analysed using chi-square test. P-value <0.05 was taken as level of significance.

4. Observation and Results

Most of the study population belonged to the age group of 26 to 35 years (53.5%) followed by 36 to 45 years (23.3%), ≤ 25 years (14%) and ≥ 46 years (9.3%).

There was male predominance (48.8%) amongst the study population as compared to females (44.2%).

Table 1. Drug resistance pattern of each individual

XDR-TB Drugs	Resistance	Frequency	Percentage
Ofloxacin	Yes	35	81.4
	NO	8	18.6
Kanamycin	YES	19	44.2
	NO	24	55.8
Cycloserine	YES	3	7
	NO	40	93
Levofloxacin	YES	2	4.7
	NO	41	95.3
Moxifloxacin	YES	6	14
	NO	37	86
Capreomycin	YES	1	2.3
	NO	42	97.7
Ethambutol	YES	3	7
	NO	40	93

Table 1 Continued

Amikacin	YES	5	11.6
	NO	38	88.4

From the Table 1 it can be seen that 81.4% of the patients showed resistance to Ofloxacin, while 18.6% were not resistant to kanamycin and 44.2% were resistant to the same drug. 24 patients were not resistant to Cycloserine, while three were resistant to it. 93% participants were not resistant to Levofloxacin, while 95.3% were not resistant to moxifloxacin. 86% participants were not resistant to Capreomycin and 2.3% were resistant to the same drug. 97.7% participants showed no resistance to Ethambutol, while only 7% showed any resistance to the said drug. 93% participants were not resistant to Amikacin. On this basis, it can be said that vast majority of the patients studied were not resistant to the said drugs.

This table showing maximum resistance to Ofloxacin (81.4%) followed by kanamycin (44.2%) and Moxifloxacin (14%). The least resistance was to Capreomycin (2.3%).

As per Table 2, 48.83% participants with PreXDR were resistant towards Fluroquinolone; while 20.93% were resistant towards PreXDR with second line injectable XDR. 30.23% participants showed resistance towards fluroquinolone + Second Line Injectable. On this basis, it can be said that the drug resistance patterns among patients with PreXDR is high.

The Table 3 shows that 25.58% patients has only diabetes mellitus, while 4.65% had only hypertension, 16.27% patients were suffering from both diabetes and hypertension. More than half, or 53.48% patients had no comorbidities.

In the Table 4 11.63% patients were from the upper-class socio-economic status, while 13.16% from the same socio-economic class were compliant. 18.6% participants were from the middle class, and 18.41% were compliant. A significant number of patients were from the lower class, further 68.42% participants were compliant.

5. Discussion

5.1 XDR Drug Resistant Status

The definition of XDR-TB is Tuberculosis bacteria resistant to isoniazid, rifampicin, one of the fluoroquinolones and any one of three injectable drugs, i.e. kanamycin, amikacin and capreomycin. Bedaquiline a new class of drug, diarylquinoline has been approved under conditional access through RNTCP PMDT in India. It specifically targets mycobacterial ATP synthase. The finding of study found on similar line of the study conducted by V. P.

Table 2. Drug resistance patterns

Pre XDR with floroquinolone	21	48.83%
Pre XDR with Second line injectable	9	20.93%
XDR (floroquinolone +Second line injectable)	13	30.23%
Total no.patients	43	100%

Table 3. Comorbidities and drug resistance in study population

Co morbidites	Total no of patients	Percentage
Only Diabetes mellitus	11	25.58%
Only Hypertension	2	4.65%
Diabetes + hypertension	7	16.27%
No comorbidities	23	53.48%
Total no patients	43	100%

Table 4. Socioeconomic status and drug resistance in study population

Socioeconomic status	Total No. patients(%)	No. of Defaulters (%)	No. of Compliant patients (%)
Upper class (U)	5 (11.63%)	0 (0%)	5 (13.16%)
Middle class (M)	8 (18.60%)	1 (20%)	7 (18.41%)
Lower class (L)	30 (69.77%)	4 (80%)	26 (68.42%)
TOTAL	43 (100%)	5 (100%)	38 (100%)

Myneeduetal, which concluded Ofloxacin (69%) overall highest number of resistant strains and least resistant to cycloserine (3%) other being ethionamide (39%), PAS (27%), kanamycin (20%), capreomycin (10%), amikacin (4%) and cycloserine (3%)[11]. The random prescription of quinolones may be the reason of high resistance and predicament to opt drug regimen to treat MDR-TB cases. The concurrent usage of second line ATT drugs and fluoroquinolones for other infections of respiratory tract, genitourinary tract etc., along with MDR-TB regimen may be the reason for resistance strains spread in the population. The study conducted by Singh et al in patients of Kanpur and Agra found resistance of 7% and 53% to Ofloxacin in strains of mycobacterium tuberculosis from category 1 and category 2 respectively. In our study 34% of XDR patients were resistant to two or more drugs, similar to the study of Shah et al which found 70% of XDR patients resistant to two or more second line drugs of ATT[13]. This proves the unchecked and widespread use of second line ATT drugs.

5.2 Comorbidities and Drug Resistance

53.48% patients had no comorbidities. However, 41.86% patients were diabetics. 25.58% patients were purely diabetics and 16.27% patients had hypertension and diabetes. Diabetes plays risk factor to cause primary MDR-TB and lowers the rate of culture conversion of MDR patients was found in the study conducted by Salindri et al[14]. Diabetes may thus have a more important role to play in the drug resistance pattern in MDR and XDR-TB patients. Diabetes is known to have a lowered or altered immune status; this may have a hand in the increased incidences of drug resistance in such patients.

5.3 Socioeconomic Status and Drug Resistance

According to the Prasad Socioeconomic classification, the study population was been divided into Upper (U), Middle (M) and Lower (L) class.

Maximum defaulters (80%) were from the Lower class, followed by Middle class. Socioeconomic factors play an important role in deciding the compliance of the patient to therapy and thus a pivotal role in the development of drug resistance. This is in agreement with a study by Zaietal[15] showed that 95% of the patients in their study population belonged to the poor class and 80% had poor nutrition. Because of their lower literacy rates also, they discontinued treatment after feeling better or if the number of tablets increased. All these factors reduced the compliance thus leading to emergence of drug resistance.

6. Conclusion

The infrastructure strengthening along with upgrading the nationwide network to provide quality assured laboratories to detect second-line DST with simultaneous drug-resistance surveillance should be an irrepressible part of national TB control program.

Second-line drugs must be administered rationally and considerately to prevent the widespread drug resistance by physicians. In the current study, maximum resistance was seen to fluoroquinolones. The addition of second-line drugs to first line regime or failure regime should be avoided. Haphazard use of flouroquinolones for other common illnesses must be reduced.

This study shows the role played by socioeconomic status in compliance and so drug resistance. This factor can be addressed by proper counseling of patients to make them aware of the disease and hazards of irregular drug use. Continuance of programmatic management of the Government scheme and regular follow-up of patients will help to reduce drug resistance in all strata' of society.

This study also underlines the importance of strict diabetes control for reducing the emergence of drug resistance.

Future large scale meta-analytic studies should be undertaken to find the prevalence of drug resistance in XDR–TB.

Implementation of effective measures towards reducing the spread of drug resistance will help alleviate the burden of TB on society as well as the Government.

7. References

1. Mesfin EA, Beyene D, Tesfaye A, Admasu A, Addise D, Amare M, Dagne B, Yaregal Z, Tesfaye E, Tessema B. Drug-resistance patterns of Mycobacterium tuberculosis strains and associated risk factors among multi drug-resistant tuberculosis suspected patients from Ethiopia. PLoS One. 2018 Jun 4; 13(6):e0197737. PMid: 29864118 PMCid: PMC5986145. https://doi.org/10.1371/journal.pone.0197737.
2. World Health Organization. Global Tuberculosis control surveillance, planning, financing; WHO report 2010; Geneva; World Health Organization WHO/HTM/TB/2010.393. Geneva, Switzerland: WHO. 2010.
3. Central TB Division. TB India 2010: RNTCP status report. Nirman Bhavan, New Delhi, India: Directorate of General Health Services, Ministry of Health and Family Welfare, 2006. Revised National TB Programme, TB India. TB India 2010. http://www.tbcindia.org.AccessedJuly2010.
4. Ahmad N, Javaid A, Sulaiman SA, Ming LC, Ahmad I, Khan AH. Resistance patterns, prevalence and predictors of fluoroquinolones resistance in multidrug resistant tuberculosis patients. Brazilian Journal of Infectious Diseases. 2016 Feb; 20(1):41–7. PMid: 26626164. https://doi.org/10.1016/j.bjid.2015.09.011.
5. Sharma SK, Chaubey J, Singh BK, Sharma R, Mittal A, Sharma A. Drug resistance patterns among extra-pulmonary tuberculosis cases in a tertiary care Centre in North India. The International Journal of Tuberculosis and Lung Disease. 2017 Oct 1; 21(10):1112–7. PMid: 28911354. https://doi.org/10.5588/ijtld.16.0939.
6. Heyckendorf J, Andres S, Koser CU, Olaru ID, Schon T, Sturegard E, Beckert P, Schleusener V, Kohl TA, Hillemann D, Moradigaravand D. What is resistance? Impact of phenotypic versus molecular drug resistance testing on therapy for multi-and extensively drug-resistant tuberculosis. Antimicrobial Agents and Chemotherapy. 2018 Feb 1; 62(2). PMid: 29133554 PMCid: PMC5786814. https://doi.org/10.1128/AAC.01550-17.
7. Ullah I, Javaid A, Tahir Z, Ullah O, Shah AA, Hasan F, Ayub N. Pattern of drug resistance and risk factors associated with development of drug resistant Mycobacterium tuberculosis in Pakistan. PloS One. 2016 Jan 25; 11(1):e0147529. PMid: 26809127 PMCid: PMC4726587. https://doi.org/10.1371/journal.pone.0147529.
8. Kim CK, Shin SY, Kim HJ, Lee K. Drug resistance patterns of multidrug and extensively drug-resistant tuberculosis in Korea: Amplification of resistance to oral second-line drugs. Annals of Laboratory Medicine. 2017 Jul 1;

37(4):323–6. PMid: 28445012 PMCid: PMC5409022. https://doi.org/10.3343/alm.2017.37.4.323.

9. Shah I, Shah F. Changing prevalence and resistance patterns in children with drug-resistant tuberculosis in Mumbai. Paediatrics and International Child Health. 2017 Apr 3; 37(2):135–8. PMid: 27686119. https://doi.org/10.1080/20469047.2016.1214796.
10. Dean AS, Cox H, Zignol M. Epidemiology of drug-resistant tuberculosis. Strain variation in the Mycobacterium tuberculosis complex: Its role in biology, epidemiology and control. (pp. Springer, Cham. 2017. p. 209–20. PMid: 29116637. https://doi.org/10.1007/978-3-319-64371-7_11.
11. MyneeduVP, Visalakshi P, Verma AK, Behera D, Bhalla M. Prevalence of XDR-TB cases –A retrospective study from a tertiary care TB hospital. Indian J Tuberc. 2011; 58:54–9.
12. Lan Y, Li Y, Chen L, Zhang J, Zhang H. Drug resistance profiles and trends in drug-resistant tuberculosis at a major hospital in Guizhou Province of China. Infection and Drug Resistance. 2019; 12:211. PMid: 30666136 PMCid: PMC6330984. https://doi.org/10.2147/IDR.S188538.
13. Sinha P, Srivastava GN, Gupta A, Anupurba S. Association of risk factors and drug resistance pattern in tuberculosis patients in North India. Journal of Global Infectious Diseases. 2017 Oct; 9(4):139. PMid: 29302148 PMCid: PMC5750437. https://doi.org/10.4103/jgid.jgid_167_16.
14. Argita D. Salindri, Maia Kipiani, Russell R. Kempker,Neel R.Gandhi, Lasha Darchia, Nestani Tukvadze, Henry M.Blumberg, Matthew J. Magee. Diabetes Reduces the Rate of Sputum Culture Conversion in Patients With Newly Diagnosed Multidrug-Resistant Tuberculosis. Open forum of infectious diseases. 2016 Jun1 14; 1.
15. Saira Zai, Tyaba Haroon, Khawaja Tahir Mehmood. Socioeconomic Factors Contributing to Multidrug-Resistant Tuberculosis. Biomed Sci and Res. 2010; 2(4):279–83.
16. Mogashoa T, Melamu P, Derendinger B, Ley SD, Streicher EM, Iketleng T, Mupfumi L, Mokomane M, Kgwaadira B, Rankgoane-Pono G, Tsholofelo TT. Detection of second line drug resistance among drug resistant Mycobacterium Tuberculosis Isolates in Botswana. Pathogens. 2019 Dec; 8(4):208. PMid: 31661825 PMCid: PMC6963291. https://doi.org/10.3390/pathogens8040208

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