Diagnostic Efficacy Of Gene X-Pert/ MTB-RIF Assay And Its Implication For The Treatment Of MDR TB In Rural Medical College

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Abstract : Aims and objectives: To diagnose and treat the MDR Tuberculosis by XPERT MTB/RIF assay as early as possible so that transmission of infection can be minimized and To find out prevalence of MDR TB in our rural district of Maharashtra. Methods: This is a observational ,prospective study conducted over a period of 14 months (Jan 15 to April 16) in the Dept. of Pulmonary Medicine, Shri Vasantrao Naik Gov.t Medical College, Yavatmal, Maharashtra. We have subjected 613 patients who fulfill the clinical criteria for RNTCP - MDRTB suspect 1.Treatment failure. 2. Retreatment case sputum positive at the end of 4 months, 3.Contact of known MDRTB case, 4.Sputum positive at diagnosis, retreatment case, 5. Any follow up sputum positive, 6.Other category (sputum negative retreatment cases), and 7. HIV-TB Cases. We have excluded all new cases (sputum positive, sputum negative and extrapulmonary cases). With all precautions two sputum samples collected in the designated microscopy centre. One sample was subjected for routine ZN staining and other one for GENE X-PERT MTB/RIF assay. Result. Out of 613 MDR suspect subjects, 314 (51.23%) were found in the age group 30 to 50 which is economically productive age group. There were 428 (69.82%) male and 185 (30.18%) female. Out of total study patient 44 (7.18 %) were detected Rifampicin resistance by X-PERT MTB/RIF assay. Amongst MDR suspect criteria highest no (4.07 %) of Rifampicin resistant were found in Retreatment cases (group 4) followed by 1.47 % in any follow up sputum positive (group 5) , 0.65 % in sputum negative retreatment cases (group 6), 0.32 % in treatment failure (group 1) , 0.49 % in HIV TB cases (group7 and0.16 % in contacts of known MDR (group 3) .There were 144 (23 .5) were co infected with HIV.TB. Conclusion: We conclude that GENE XPERT MTB /RIF assay has significant role in detecting Rifampicin resistance, patient can be started on treatment at the earliest thereby reducing morbidity, progression to XDR, mortality and transmission of MDR/XDR TB in the community can be minimized. However it has some shortcomings that it cannot detect resistance of other anti- tubercular drugs and atypical mycobacteria.[B.B.Bhadke NJIRM 2016; 7(5):33-39]

Key words: GENE XPERT MTB/RIF assay. Rifampicine resistance, MDR TB, HIV TB.

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Introduction : The newer tests for diagnosing Tuberculosis (TB) are needed because of the difficulties associated with the test that are currently used both to diagnose as well as to detect drug resistance. Traditionally TB has been diagnosed through the use of chest X- ray, smear microscopy and through the culture. One of the most significant disadvantage of culture being the time that it takes and for sputum the matter of accuracy.[1]

Multidrug resistance is an increasing concern globally and directly threatens disease-control efforts in many countries. Globally, 3.6 % of new TB cases and 20.2 % of previously treated cases are estimated to have MDR TB. In India Prevalence of MDR TB has been estimated to be 1-3 % and 12-14% in new and previously treated cases respectively.[(5)] Every year nearly 5,00,000 new cases of multidrug resistance tuberculosis are detected and reported, and mis-diagnosis causes thousands of deaths, nosocomial and community transmission, and amplification of drug resistance.[1,2,3]

To resolve these issues, substantial efforts are being made to strengthen laboratory capacity to diagnose smear negative and multi drug resistance tuberculosis, including increased use of solid and liquid culture, conventional drug-susceptibility testing and line probe assays. Unfortunately, these tests requires extensive laboratory infrastructure and cannot be done outside of reference facilities and also it is not feasible in rural areas.[4,5]

Recently, a real time PCR assay (MTB/RIF) that simultaneously detects Rifampicin resistance was developed on the GeneXpert platform (Cepheid, Sunnyvale, CA,USA), which integrates sample processing and greatly simplifies testing. This Xpert MTB/RIF assay, showed excellent performance in multi center study undertaken in reference laboratories. MTB/RIF assay detects M. Tuberculosis

and RIF resistance by PCR amplification of the 81 bp fragment of the M. Tuberculosis rpoB gene and subsequent probing of this region for mutations that are associated with RIF resistance. The assay can be completed within two hours[3,4]

The aim of this study was to diagnose and treat MDR TB as early as possible so that patient can be initiated on DOTS-PLUS treatment early and morbidity ,mortality, occurrence of XDR and transmission in the community can be reduced and to find out prevalence of MDR TB in our rural district of Maharashtra.

Methods: We have subjected 613 patients over period of 14 months, from Jan 2015 – April 2016 in rural tertiary care hospital, which is a 700-beded teaching hospital with one DOTS PLUS unit and MDR-TB centre catering the 16 TB units of District. Study was conducted in Dept of Pulmonary Medicine, Shri Vasantrao Naik Govt. Medical College, Yavatmal, (Maharashtra). Which is observational, prospective study conducted after approval taken from Institutional Ethical Committee.

Clinical screening for MDR-TB suspect: The patients were enrolled in the study and group as per the RNTCP MDR suspect clinical criteria.

Table 1 Clinical criteria for RNTCP MDR suspect

Patient Group	Clinical criteria
Group 1	Treatment failure
Group 2	Retreatment case sputum positive at 4 months.
Group 3	Contact of known TB.
Group 4	Sputum positive at diagnosis, retreatment case
Group 5	Any follow up sputum positive
Group 6	Other category (sputum negative retreatment cases)
Group 7	HIV TB cases

We have excluded all new cases (sputum AFB positive and sputum AFB negative and extra pulmonary new cases) as per RNTCP norms.

MDR-TB Confirmation: All the study patients with clinically suspected MDR-TB criteria have been referred to X-pert MTB/RIF assay lab which is under dept of Microbiology. With all precautions two sputum specimens collected from the patients in the designated microscopic centre. One sputum sample was subjected for ZN staining and other for X-pert MTB/RIF assay.

The X-pert MTB/RIF assay: X-pert MTB/RIF cartridge labeled with the corresponding specimen ID.1.0 ml expectorated sputum transferred to a conical, screw-capped tube using a sterile transfer pipette. 2.0 ml X-pert MTB/RIF Sample Reagent (2:1; v/v) added to the expectorated sputum using a sterile transfer pipette. The lid was replaced, and tube shaken vigorously for 10-20 times. The tube allowed to stand upright for 5 min at room temperature and again the tube was shaken vigorously for 10-20 times. The tube was allowed to stand upright for another 10 min at room temperature. Then specimens inspected as samples should be allowed to liquefied with no visible clumps of sputum. The X-pert MTB/RIF cartridge lid was opened. Using the sterile transfer pipette provided, aspirated the liquefied specimen into the transfer pipette until the meniscus is above the minimum mark and transferred the sample into the open port of the X-pert MTB/RIF cartridge. Closed the cartridge lid and test started as per Gene X-pert Dx System manufacturer instruction.

The X-pert MTB/RIF assay results representative: Each X-pert MTB/RIF cartridge includes reagents for the detection of MTB complex and RIF resistance as well as a sample processing control (SPC) to control for adequate processing of the target bacteria and to monitor the presence of inhibitor(s) in the PCR reaction.

The Probe Check Control (PCC) verifies reagent rehydration, PCR tube filling in the cartridge, probe integrity, and dye stability.[6] The primers in the X-pert MTB/RIF assay amplify a portion of the *rpoB* gene containing the 81 base pair "core" region. Five differently colored fluorogenic nucleic acid hybridization probes, called molecular beacons, interrogate the entire 81-bp core.[7] Each molecular beacon was designed to be so specific that it does not bind to its target if the target sequence differs from the wild-type *rpoB* sequence by as little as a single nucleotide substitution. Since molecular beacons fluorescence only when they are bound to their targets, i.e. wild type *rpoB* sequence, the absence of any one of the five colors in the assay differentiate between the conserved wild type sequence and mutations in the core region that are associated with RIF resistance.[8]

The SPC should be positive in a negative sample and can be negative or positive in a positive sample. The test result will be "Invalid" if the SPC is not detected in a negative test. Before the start of the PCR reaction, the Gene X-pert Dx System measures the fluorescence signal from the probes to monitor bead rehydration, reaction tube filling, probe integrity and dye stability. The PCC passes if the fluorescence signal from the probes meets the assigned acceptance criteria. The results are interpreted by the Gene X-pert Dx System from measured fluorescence signals and embedded calculation algorithms and are displayed in the View Results window[9], as indicated below:

MTB Detected: MTB target DNA is detected; both controls, SPC and PCC, meet the assigned acceptance criteria. Lower Ct values represent a higher starting concentration of DNA template; higher Ct values represent a lower concentration of DNA template. In MTB DETECTED results "RIF Resistance DETECTED","RIF Resistance NOT DETECTED", or "RIF Resistance INDETERMINATE" will display on a separate line.

MTB Not Detected: MTB target DNA is not detected; both controls, SPC and PCC, meet the assigned acceptance criteria.

Invalid: Presence or absence of MTB cannot be determined: SPC does not meet acceptance criteria, i.e. the sample was not properly processed, or PCR was inhibited All the samples were subjected for Gene expert assay those who have found resistance for Rifampicin were subjected for culture and anti-TB drug resistance (DRT). Before we get result of culture DRT MDR patients were put on category 4 regimens. That reduced the time for starting MDR treatment there by reducing the transmissions of MDR bacilli in the society.

Statistical Analysis: Statistical analysis was performed with the spss for window (version 16.0) software package. Numerical variables were summarized with mean +_ standard deviation. The significance of differences among groups was assessed by the student test and analysis of categorical variables was examined by the chi square test. A value of P of <0.05 was considered significant for all statistical analysis.

Results : Total 613 clinically suspected patients were enrolled in the study. Highest Number of patients found in the age group of 30-50 years which is most economically productive age group and males were as usual dominate gender which has been affected .Patients from retreatment group were diagnosed as highest MDR patient.

Table 2: Age Wise Distributions Of Patients

Sr. No	Age group	No of Patients
1	1-10	06 (0.98%)
2	11-20	53 (8.64%)
3	21-30	129 (21.04%)
4	31-40	204 (33.28%)
5	41-50	110 (17.95%)
6	51-60	73 (11.90%)
7	61-70	32 (5.22%)
8	71-80	06 (0.98%)

Table 3: Sex Distribution Of Patients

Sr. No	Gender	No of Patients.
1	Male	428 (69.82%)
2	Female	185 (30.18%)

Table 4: Showing MDR Detected And Not Detected In Clinically Suspected Patients

Sr. No	RNTCP MDR suspect criteria	No of Pts	MDR detected	MDR not detected
1	Treatment failure	8 (1.30%)	2 (0.32%)	6 (0.98%)
2	Retreatment case sputum positive at 4 months.	2 (0.32%)	0	2(0.32%)
3	Contact of known MDR.	3(0.49%)	1(0.16%)	2(0.33%)
4	Sputum positive at diagnosis , retreatment case	283(46.16%)	25(4.07%)	258 (48.08%)
5	Any follow up sputum positive	56 (9.13%)	9 (1.47%)	4 (7.67%)
6	Other category (sputum negative retreatment cases)	117 (19.08%)	4 (0.65%)	113 (18.43%)
7	HIV TB cases.	144(23.5%)	3 (0.49%)	141(23%)
	Total	613	44 (7.18%)	569 (92.82%)

Discussion: Globally, ineffective tuberculosis detection and the rise of multidrug resistance and extensively drug resistance tuberculosis has led to calls for dramatic expansion of cultural capability and drug susceptibility testing in countries like India in which the disease is endemic.[10] Unfortunately the infrastructure and trained personnel required for such testing are not available in rural part of India except in a limited number of reference center, and results of testing are often not available for at least 4 months, which dramatically reduces its clinical utility. And also accelerates the disease transmission in the society. These short comings have been rectified by recently introduced Gene-Xpert MTB/RIF assay.

Table 5: Showing HIV TB Co-Infection

Sr. No	HIV status	No of Patients
1	HIV reactive	144 (23.5%)
2	HIV nonreactive	469 (76.5%)

We have subjected total 613 patients, 428 (69.82%) were male & 185 (30.18%) were female with ratio 2.3:1,(Table 3) having mean age were 37.21year with more prevalence in 20-50 year(Table 2). Various reasons have been suggested to explain the gender imbalance. Less access to health care for women, and therefore more unreported TB, has been mentioned in many countries,[11]and the potentially less sensitive screening and diagnosis strategies for women has led to underestimation of TB in women [12]. Other explanations such as social behavior among men and the difference between male and female susceptibility to TB have also been mentioned.[13] It has been observed in several settings that women have better health seeking behavior compared to men and that men have more advanced symptoms by the time they seek healthcare.[14] MDR-TB patients were more likely to be younger than 65 years. The pooled risk of MDR-TB for people younger than 45 was lower. Only five of the eight studies [13,15,16,17,18] that analyzed age under 45 found an association, and the heterogeneity remained very high.The studies showed that patient's age, gender and race have no correlation with drug-resistant tuberculosis occurrence. It means that drug-resistant tuberculosis can happen in every age, gender and race.[19] Our study shows similar results with these studies.The world health organization has documented MDR TB worldwide. .In present study we examined total 613 patients satisfying the criteria for WHO recommending MDR TB testing on Gene X-pert MTB/RIF assay .[20] In current study we have found the prevalence of MDR TB 7.18% in high risk group of population.

Chowgule et. al[21] Mumbai have consistently shown higher levels of MDR TB than in other parts of India , at 24% -30% of new cases [22] and 11-67% of treated cases [23]. Negi et al [24] has shown corresponding figures from other parts of the country are 1%-13% & 12%-40% respectively. Sanchez-Padilla E et al[25] in their study at Switzerland, has shown 7.7% & 33.8% of TB smear positive new cases & previously treated cases , respectively, had MDR TB . This represents an 8.5 fold & 3.7 fold increase compared with MDR prevalence among new cases& previously treated cases respectively.[25] So, early detection of drug resistant and assessment of various factors that may increase the likelihood of drug resistant in tuberculosis is important.

The World Health Organization stated that in most of the world, more men than women are diagnosed with tuberculosis and die from it. The global male to female prevalence ratio of tuberculosis is 1.85. [26]

In present study among 613 patients, 144 (23.5 %) patients were HIV reactive and 469 (76.5%) were HIV nonreactive. Among the 144 (23.5%) HIV positive patients only 3 (0.49%) were MDR - TB. Corbett et al.[27] has studied the association between HIV & TB. In their study they have shown that HIV co-infection is the most potent immunosuppressive risk factor for developing active TB disease. HIV co-infection greatly increases the chances of reactivation of latent infection of TB [28] and increases the rapid TB progression following primary infection or re-infection with TB. [29] Individual studies conducted in both high[30] and low burden TB countries [31] have attributed increasing TB incidence to HIV infection. Our study also shows the significant association between HIV & TB like previous studies. But the correlation between HIV infection and drug resistance TB remains controversial. According to Cohn et al, 1997 [32], though the association of MDR TB with AIDS has been well documented during outbreaks,[33] the role of HIV infection as a risk factor for the development of drug resistant TB in other settings was not clear.[34] In Kenya, Malawi, Tanzania, Cote d'Ivoire, and France, drug resistance was not associated with HIV infection.[35] Robert et al[36] in their study from France and Girardi et al [37] in Italy did not find any association with this variable. In contrast, study done by Gordin et al [38] in a

survey of eight metropolitan areas of the United States, HIV infection was associated with resistance to drug resistant TB, both within and outside the New York City area.

Mal-absorption of anti-TB drugs has been documented for HIV-reactive patients, which could increase the risk for acquired Rifampicin resistance [39] In settings where HIV infection is linked to socioeconomically vulnerable populations, poor treatment adherence and lack of access to proper treatment may contribute to the development of drug resistance.[40] In our study we found HIV co-infection was independently associated with MDR TB.

In present study among 613 patients, we have found 8(1.30%) treatment failure, of which 2 (0.32%) had MDR –TB positive, retreatment case 283(46.16%) of which 25(4.07%) MDR-Positive. The study of Jeon et al, 2011[41], shows that inadequate treatment has contributed to the high prevalence of MDR and XDR-TB. In Korea, the prevalence of MDR-TB has been estimated to be up to 10 times higher after unsuccessful treatment.[42] Our study shows similar results with these studies. Delayed diagnosis, delayed recognition of drug resistance, inappropriate chemotherapy regimens, inadequate or irregular drug supply, and poor compliance by both patients and clinicians have each been reported as a reason for inadequate treatment.[42] A few studies in review specified the reasons for inadequate treatment for example, defaulting treatment received previously, treatment in prison, and being given fewer than four drugs.[42]In our study among total sample 3(0.49%) patients had history of family contact of which 1 (0.16%) MDR-TB positive. TB prevalence among contacts is very high.[43] The odds ratio of having a family member with TB and developing TB is estimated at 13.4 further highlighting the importance of close TB contact and TB risk.[43] Data from a recent study confirm that the MTB/RIF assay generates no infectious aerosol. These features of simplicity and safety of use could allow for cost effective and highly sensitive detection of tuberculosis and drug resistance outside reference center, which would increase access to testing and decrease delays in diagnosis, without the need to build large numbers of laboratories equipped for advanced bio-safety.

Conclusion: we conclude that GENE XPERT MTB /RIF assay has significant role in detecting Rifampicin resistance. patient can be started on treatment at the earliest thereby reducing morbidity, progression to XDR, mortality and transmission of MDR/XDR TB in the community can be minimized. However, it has some shortcomings that cannot detect resistance of other anti tubercular drugs and atypical mycobacterium.

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