

Pattern of Drug Resistance in Previously Treated Patients of Pulmonary Tuberculosis – A Scenario in Tertiary Care Hospital

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ABSTRACT

Introduction: Drug resistance is defined as the temporary or permanent capacity of the organisms and their progeny to remain viable or multiply in the presence of concentration of the drug that would normally destroy or inhibit the growth of other cells. Study aimed to see the acquired drug resistance pattern to anti-TB drugs in Goa.

Material and methods: The sputum smear and culture for Mycobacterium Tuberculosis and drug sensitivity tests were performed in 196 patients who had received anti-TB treatment for more than 4 months as retreatment regimen. All these patients had clinical, bacteriological and/or radiological deterioration. The sputum smear was positive for AFB in all the patients, the sputum culture was done by LJ method and the sensitivity to Streptomycin, INH, Rifampicin Ethambutol, Kanamycin and Ethionamide was done at National Reference Laboratory, Chennai.

Results: 154 patients had culturable bacilli of which 12 patients had bacilli sensitive to all the drugs for which susceptibility tests were performed. High level of resistance was encountered with Streptomycin-73.2% (n=104), Ethambutol-73.2% (n=104) and Rifampicin -72.5% (n=103). The resistance to INH was highest at 89.4% (n=127) and to Kanamycin was least i.e. 10.5% (n=15). Surprisingly 37.2% (n=53) patients had bacilli resistant to Ethionamide though none of these patients had received the drug prior to the sensitivity tests. Resistance to more than 3 drugs was found in 62.7%.

Conclusions: High level of resistance to anti-TB drugs among previously treated patients presenting to tertiary care centre is a subject of grave concern and an indicator of the failure of treating drug sensitive tuberculosis at the peripheral centres.

Keywords: Multidrug-Resistant, Pulmonary Tuberculosis, Tertiary Care Centre

in complying with the physician instructions are the factors mainly responsible for emergence of drug resistance.³

The primary drug resistance is comparatively less common and less important. The initial drug resistance which includes concealed acquired resistance is more common. The earlier terms of primary and acquired drug resistance are now replaced by WHO and IUATLD (International Union Against Tuberculosis and Lung Diseases) as drug resistance in new cases and drug resistance in previously treated cases respectively.⁴ Hence it is important to elicit the details of previous chemotherapy with the schedule, regularity in collection as well as consumption and the total duration of treatment received. This will help not only in suspecting the presence of drug resistance but also in planning the re-treatment regimen.

The acquired INH resistance varied from 17% in Czechoslovakia to 71% in Spain.⁵ In National Drug Resistance Survey carried out by ICMR; Nagpur had 22% resistance during 1968-69, while Kolkata registered the highest figure of 74%.^{6,7} The rising trend has been highlighted by Baldev Raj et al⁸ who noted that acquired drug resistance had risen from 54.76% to 81.48% during 1980-89.

Based on WHO and IUATLD Guidelines⁹ a total of 72 surveillance projects on anti-TB drug resistance have been completed in 65 countries during 1994–99. Among previously treated cases the median prevalence of resistance to any drug was 33.4%.

The Department of Pulmonary Medicine of Goa Medical College is a referral centre catering to the need of the State of Goa as well as neighboring districts of Karnataka and Maharashtra. There has not been any study depicting the acquired drug resistance pattern to anti-TB drugs in Goa. Hence we undertook the present study.

MATERIAL AND METHODS

Study was done in Department of Pulmonary Medicine of Goa Medical College. All the 196 patients admitted to the Department of Pulmonary Medicine of Goa Medical College, Goa with following features were included in the study.

1. Those patients who had received anti-TB treatment for

INTRODUCTION

Drug resistance is defined as the temporary or permanent capacity of the organisms and their progeny to remain viable or multiply in the presence of concentration of the drug that would normally destroy or inhibit the growth of other cells.¹ The genetic mutation and the adaptation of Mycobacterium TB to the drugs, ignorance of the prescribing physician and failure of the patients in complying with the physicians instructions are the factors mainly responsible for emergence of drug resistance.² According to Mitchison, it is a decrease in sensitivity to the drug of a sufficient degree to be reasonably certain that the strain concerned is different from a sample of wild strains that have never been in contact with drugs.³

The emergence of drug resistance, especially MDR-TB poses a major problem in the control of tuberculosis under the Revised National Tuberculosis Control Program. The genetic mutation and the adaptation of Mycobacterium TB to the drugs, ignorance of the prescribing physician and failure of the patients

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4 months or more of retreatment regimen and who were symptomatic with fever, loss of weight and appetite.

- Who were positive for AFB by smear and/or culture method.
- Who showed radiological deterioration.

Since we did not have facilities for performing sensitivity tests to anti-TB drugs during the study period the samples were sent through private couriers to NIRT (erstwhile TRC), Chennai; taking all necessary precautions for transit period. No anti-TB drugs were administered at least 96 hours prior to collecting the sputum for culture and sensitivity tests. The sputum was collected in two wide mouthed autoclaved screw capped bottles. The transit time was usually 24 hours.

At TRC, the sensitivity tests were performed for streptomycin, INH, ethambutol, rifampicin, kanamycin and ethionamide.

STATISTICAL ANALYSIS

Statistical analysis was done with the help of Microsoft office 2007. Mean and percentages were used for the analysis of data.

RESULTS

Sputum samples of 196 patients were sent for AFB culture and sensitivity tests. 11 patients were positive on smear examination, but were negative by culture method. 31 patients sputum samples were negative by smear as well as culture method. The sensitivity pattern of 154 patients was thus available for study. 12 of them had bacilli sensitive to all the drugs for which the sensitivity tests were carried out at TRC. 142 patients had bacilli showing resistance to one or more drugs (Table 1).

The pattern of resistance to one or multiple drugs is shown on detail in Table 2.

The number of patients excreting bacilli resistant to three or more drugs were very high (78.4%) with 62.7% of them being resistant to more than three drugs. The pattern of resistance of individual drugs is shown in Table 3.

89.4% patients carried bacilli resistant to INH. The resistance to rifampicin and ethionamide was alarmingly high (72.5% and 37.2% respectively). The picture is all the more gloomy as none of these patients had received ethionamide prior to admission to the study (table 4).

The percentage of MDR-TB stains in the present study was remarkably high (71.1)

DISCUSSION

Acquired drug resistance is on the rise globally. An estimated 3.3% of new cases and 20% of previously treated cases have MDR-TB: these levels sadly have remained unchanged in recent years. In 2014 there were estimated 480,000 new cases of MDR-TB, and approximately 190,000 deaths from MDR-TB worldwide.¹⁰ In Hongkong more than 20% of the strains are said to be resistant to one or more drugs.¹¹ In India, during the I.C.M.R. National Drug Resistance Survey^{6,7} the acquired drug resistance was 22% in Nagpur, whereas in Kolkata it was 74%. The total prevalence of drug resistance to one or more anti-TB drugs among patients attending DTC for the first time was 54.5% in Chennai.¹² The data from studies conducted by NIRT (erstwhile TRC) and NTI have found MDR TB levels of 1% to 3% in new cases and 12% in retreatment cases.^{13,14} Even if the present study does not reflect the true prevalence of drug resistance in general population, it reflects the worrying

	Bacteriological status	Number	Percentage
1.	Smear positive culture positive	146	74.5
2.	Smear negative culture positive	8	4.1
3.	Smear positive culture negative	11	5.6
4.	Smear negative culture negative	31	15.8
Total		196	

Table-1: Smear and culture status of the patients

		Number	Percentage
1.	Resistant to one drug	14	9.8
2.	Resistant to two drugs	16	11.3
3.	Resistant to three drugs	23	15.7
4.	Resistant to more than three drugs	89	62.7
Total		142	

Table-2: The pattern of resistance to one or multiple drugs

		Number	Percentage
1.	Streptomycin	104	73.2
2.	INH	127	89.4
3.	Ethambutol	104	73.2
4.	Rifampicin	103	72.5
5.	Kanamycin	15	10.5
6.	Ethionamide	53	37.2

Table-3: Resistance pattern of individual drugs.

		Number	Percentage
1.	MDR – TB strains	101	71.1
2.	Non MDR strains	41	28.9
Total		142	

Table-4: MDR -TB strains

situation at the tertiary level and needs attention on priority. Though clinically suspected to be resistant cases, 8(4.1%) patients in the present study were smear negative but positive by culture. Thus relying solely on smear examination to label a patient as drug resistant PTB can lead to many a cases being missed and denied the required treatment. 11(5.6%) patients exhibited smear positive but culture negative phenomena. All these patients had clinical or radiological deterioration following anti-TB therapy for 4 months or more of retreatment regimen. This could be attributed to a) prolonged transit time and b) exposure to unfavourable conditions in transit rendering the bacilli non-culturable. Similar observation was made by Vasant Kumari et al¹² but since their population contained patients presenting for the first time to DTC irrespective of their previous chemotherapy, they attributed it to dead bacilli. The acquired resistance to individual drugs too has been of much concern. The world literature shows that acquired INH resistance has been varying from 17% in Czechoslovakia to 71% in Spain.⁵ The upward trend had been documented in Haryana where it increased from 43.52% during 1980-84 to 64.81% during 1985-89.⁸ High level of INH resistance (89.4%) observed in this study substantiates the rising trend. When Rifampicin was introduced in seventies it was considered to be the wonder drug capable of destroying even the toughest of M. tuberculosis strains. The repercussion of indiscriminate and irregular administration of the drugs by the general practitioners as well as the ever flourishing fleet of quacks are being felt. In a survey conducted in Gujarat acquired Rifampicin resistance

increased from 2.8% in 1980 to 37.3% in 1986. In 95% of these cases, the strain was also resistant to INH, streptomycin or both.¹⁵ A five fold rise in five years from 3.17% to 17.89% was observed in Haryana.⁸

A single time-point cross sectional survey carried out by TRC Chennai in a cohort of 3,357 smear positive cases in North Arcot district found the frequency of acquired drug resistance to be 67% to INH, 12% to Rifampicin and 11% to both INH and Rifampicin.¹⁶ In a recently conducted study in Bengaluru, the multi-drug resistance in previously treated cases was found to be 12.8% (8.4-17.2%).¹⁷

XDR-TB, defined as MDR-TB plus resistance to at least one fluoroquinolone and a second line injectable drug (aminoglycoside) had been reported by 105 countries globally by the end of 2014.¹⁰ Lee et al observed MDR-TB and XDR-TB in 5.8% and 2.0% of new cases and in 20.1% and 8.6% of previously treated cases in a study done in a tertiary care centre in Korea which included patients with pulmonary and extrapulmonary TB.¹⁸ Similarly increasing incidence of fluoroquinolone resistance in pulmonary TB patients has been reported by Agrawal et al¹⁹ and this has been due to indiscriminate use of respiratory quinolones for treatment of community acquired pneumonia. We would like to make a special mention of resistance pattern to ethionamide which was alarmingly high i.e. 37.2% (n=53). The scenario has been particularly worrying as none of these patients had received ethionamide earlier. Of these 7.7% (n=11) had received thiacetazone in the peripheral centres several years ago. This could possibly be the cause for ethionamide resistance as the two are known to exhibit cross resistance. Furthermore 10.5% (n=15) had bacilli resistant to Kanamycin, the cause of which could not be explained as none of these patients had received kanamycin earlier. Lastly the possibility of genetic mutation cannot be ruled out.

Multiple drug resistance in tuberculosis i.e. MDR-TB has become the new buzz word in the world of tuberculosis workers. In New York the resistance to one or several drugs among HIV infected previously untreated tuberculosis patients has risen from 10% to 23% in the last decade. In U.S.A as a whole nearly 90% of MDR is found among HIV seropositive tuberculosis patients with case fatality of around 70% in four to sixteen weeks time, while case fatality among non-HIV/MDR is as high as 25%.²⁰ Since we do not have HIV status of our patients in the study group it is not appropriate to comment on this aspect. However the MDR-TB strains isolated in the present study were very high i.e. 71.1% which should be the cause of serious concern.

The number of patients excreting bacilli resistant to more than three drugs is on the rise in India too (10% to 29%).^{8,3} Nagaraja C et al observed that the resistance to all the first line drugs was found in 65.2% patients in a study done at a tertiary care centre and included 224 cases of MDR-PTB patients²¹ The present study has also revealed high figure (62.7%).

CONCLUSION

Though this high level of resistance is not indicative on the prevalence of MDR or XDR in general population, it is still a matter of concern as the economic burden of treating these cases is huge. All efforts should be made to ensure uninterrupted and complete treatment of patients with drug sensitive bacilli to prevent emergence of drug resistance.

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