Original Article

PREVALENCE OF XDR TB CASES – A RETROSPECTIVE STUDY FROM A TERTIARY CARE TB HOSPITAL

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Summary

Background: The emergence of XDR –TB strains is a major roadblock in the successful implementation of TB control programmes. This further leads to high morbidity and mortality, especially in immuno-compromised patients. Identification and observation of resistance patterns of XDR-TB strains may help clinicians manage MDR-TB cases, the treatment line of which is expensive, time-taking and involves intake of toxic drugs with many side-effects. Our study is aimed to find out the prevalence of XDR-TB among the MDR-TB strains isolated in a tertiary care hospital.

Material & Methods: The study population consisted of 223 patients of tuberculosis who were culture positive and *Mycobacterium tuberculosis* was resistant to Rifampicin and Isoniazid during January 2007 to December 2009. Each patient had submitted two sputum samples i.e. spot and morning. The identified *Mycobacterium tuberculosis* complex was subjected to drug sensitivity testing by first and second line drugs by proportion and absolute concentration methods as per standard procedure .

Results : The results showed that 20.17% strains (45/223) were XDR-TB strains. Most of these strains showed resistance to four drug combination viz. KM, ETH, OFX & PAS (5.82%), KM & OFX (3.13%), OFX, KM and ETH (1.79%), 1.34% strains showed resistance to all the drugs i.e. pan resistance and other combinations in the remaining strains. Nearly 80% of the XDR-TB strains showed resistance to three or more drugs combination pattern.

Conclusion: The multidrug resistant TB cases need urgent and timely sensitivity report for second line ATT drugs to help clinicians start proper drug combinations to treat MDR-TB patients. ***[Indian J Tuberc 2011; 58:54-59]***

Key words: *Mycobacterium tuberculosis*, Multi Drug Resistant TB (MDR-TB), Extensively Drug Resistant TB (XDR-TB), Drug sensitivity testing, Proportion method

INTRODUCTION

Tuberculosis, a well-known bacterial disease for the last 5000 years, is still infecting nearly one-third of world population with a daily addition of 5000 new cases and loss of two lives every third minute[1]. In India, 1.9 million new cases are reported every year, of which 0.8 millions are 'infectious smear positive TB cases'. According to WHO, death rate due to TB in India is nearly 28 per 1,00,000 population, which is the highest death rate among all other communicable diseases and accounts for 26 per cent of all avoidable adult deaths[2].

The previous studies in India showed that three per cent of MDR-TB is seen in new tuberculosis cases and 17.2 per cent among retreatment cases. Ramachandran *et al* had reported 3.2% of XDR strains among the MDR isolates in a field study from Gujarat[3-5]. Information related to MDR-TB is showing relatively less number of cases but what is frightening is the number of XDR-TB cases, which is really a potential threat to healthy population of India.

In countries like India, most clinicians are not adhering to the antibiotics policy and are rampantly using second line drug treatment even in the absence of sensitivity reports. Such a malpractice may culminate in the outbreak of TB and newer TB strains, viz. XDR-TB strain, etc., beyond control. The emergence of XDR-TB strains is threatening the commitment underlying the DOTS Plus programme that intends to provide high quality service in diagnosis and treatment of MDR-TB.

XDR-TB is defined as strain of *Mycobacterium tuberculosis* resistant to isoniazid,

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rifampicin, one of the fluoroquinolones and any one of three injectible drugs, i.e. kanamycin, amikacin and capreomycin[6,7]. The drug sensitivity test data showed that XDR strains are prevalent all over the world except Antarctica and many more reports are coming in recent years[8]. According to available second line antituberculous drug sensitivity reports, the prevalence of XDR-TB cases amongst the MDR-TB varies from 5% - 15% around the world [9.10]. There is paucity of reports showing XDR-TB cases from India. The DST report mostly by non-accredited laboratories from India showed 5-16 per cent XDR-TB strains among MDR-TB strains[11]. Our accredited laboratory is carrying out DST for first line ATT drugs for the last 10 years and second line ATT drugs for the last three years.

This study is an attempt to find out the true prevalence of XDR-TB cases among the MDR-TB patients.

MATERIAL AND METHODS

It is a retrospective study conducted by Department of Microbiology of Lala Ram Swarup Institute of TB and Respiratory Diseases in New Delhi. The study population consisted of 223 patients of tuberculosis who were culture positive and *Mycobacterium tuberculosis* was resistant to rifampicin and isoniazid during January 2007 to December 2009. Each patient had submitted two sputum samples i.e. spot and morning according to the RNTCP guidelines. The culture was done on Lowenstein-Jensen (LJ) media following decontamination and concentration by modified Petroff's method[12]. The positive cultures were identified by niacin test, catalase test and sensitivity to PNB test. The identified *Mycobacterium tuberculosis* complex was subjected to drug sensitivity testing by first line drugs viz. isoniazid (H),rifampicin (R), pyrazinamide (Z), ethambutol (E) and second line drugs, viz. kanamycin (KM), ethionamide (ETH), capreomycin (CPM), amikacin (AK), ofloxacin (OFX), para aminosalycylic acid (PAS), and cycloserine (CYS)] by proportion method and absolute concentration method as per standard procedure[13].

RESULTS

During the period January, 2007 to December, 2009, the randomly selected 223 MDR-TB strains were subjected to second line anti-tuberculous drugs sensitivity testing. The 223 MDR-TB isolates were tested with kanamycin, ethionamide, capreomycin, amikacin, ofloxacin, PAS, and cycloserine, which were used in the treatment of MDR-TB patients. During the sensitivity testing, 28 different resistance patterns were observed amongst the aforementioned drugs. The overall highest number of resistant strains were seen with ofloxacin (69%) followed by resistance to ethionamide (39%), PAS (27%), kanamycin (20%), capreomycin (10%), amikacin (4%) and cycloserine (3%) (Table-1).

As per WHO definition of XDR-TB[6,7], 20.17% (45/223) were considered as XDR-TB strains. Most of these strains showed resistance to four drug combination, viz. KM, ETH, OFX & PAS (13/223) followed by KM & OFX (7/223), while 3/223 strains showed resistance to all the drugs i.e. pan resistance (1.34%) used in treatment of MDR cases. Nearly 80% of the XDR-TB strains showed resistance to three or more drugs combination pattern (Table -2).

In the other second line ATT drug resistant pattern, more than four drugs resistance pattern was observed in 30 out of 223 (13.45%) MDR-TB isolates and the maximum resistance was seen in the combination of KM, ETH, OFX and PAS (5.82%) (Table-3).

Table 1: MDR TB strains resistant to second line ATT drugs [n = 223]

Drugs	No. of Resistant *M.tb* strains	Percentage of *M.tb* strains
Ofloxacin	154	69.05
Ethionamide	87	39.01
PAS	61	27.35
Kanamycin	46	20.62
Capreomycin	22	9.86
Amikacin	9	4.03
Cycloserine	7	3.13

PAS = Para-Aminosalicylic Acid
M.tb = *Mycobacterium tuberculosis*
MDR TB = Multidrug resistant tuberculosis

Table 2: Number of XDR-TB strains & its resistance pattern among the MDR-TB strains

Drug patterns	No. of Resistant strains	Percentage of Resistant strains
KM , OFX	7	3.13
KM, OFX, PAS	1	0.44
KM, OFX, ETH	4	1.79
KM, OFX, CM	2	0.89
KM, OFX, ETH, PAS	13	5.82
KM, OFX, AMK, CPM	3	1.34
KM, OFX, ETH, CPM	3	1.34
KM, OFX, AMK, CPM, PAS	1	0.44
KM, OFX, ETH, AMK, CPM	1	0.44
KM, OFX, ETH, CPM, PAS	3	1.34
OFX, CPM	2	0.89
OFX, ETH, CPM	2	0.89
All Resistant	3	1.34
Total	45	

PAS = Para-Aminosalicyclic Acid, KM = Kanamycin,
OFX = Ofloxacin, ETH = Ethionamide, CYS = Cycloserine,
CPM = capreomycin

Table 3: Second line ATT drugs resistance pattern of MDR strains

Drugs	No. of Resistant strains	%age of Resistant strains
KM	1	0.44
KM , ETH	2	0.89
KM, PAS	1	0.44
OFX	58	26.00
OFX, ETH	20	8.96
OFX, PAS	13	5.82
OFX, ETH, PAS	16	7.17
ETH	12	5.38
ETH, PAS	5	2.24
PAS	1	0.44
PAS, CYS	2	0.89
KM, ETH, AMK, CPM	1	0.44
ETH, OFX, CYS, CPM, PAS	1	0.44
ETH, OFX, CYS, PAS	1	0.44
ALL SENSITIVE	44	19.73
Total	178	

PAS = Para-aminosalicylic acid, KM = Kanamycin, OFX = Ofloxacin,
ETH = Ethionamide, CYS = Cycloserine, CPM = Capreomycin,
ATT= Antituberculosis treatment

A total of 44 (19.73%) MDR-TB strains were sensitive to all the tested second line ATT drugs (Table- 4).

Apart from the criteria met for 45/223 XDR-TB strains as already specified by WHO, we found that 79.82% (178/223) strains were resistant to other drug combinations of second line ATT drugs.

Table 4: Status of MDR strains January, 2007-December, 2009 [n = 223]

Type of Resistance	No. of Resistant samples	Percentage of Resistant samples
XDR-TB	45	20.17
Any Resistant	134	60.08
All Sensitive	44	19.73
Total	223	

Status of XDR TB reported in different research publications

Place of study	Year of study	No of MDR TB strains tested	No of XDR resistant strains (%)	Reference No
Italy	1993-2004	83	8(14.3)	9
Germany	1993-2004	43	3(10.3)	9
France	2006	_	4%	22
Iran	2006	113	12(10.9)	23
Hong Kong	2004	75	9(12.01)	24
Industrialsed nations	2000-04	821	53(6.5)	10
Eastern Europe and Russia	2000-04	406	56(13.6)	10
Republic of Korea	2000-04	1298	200(15.4)	10
India	2006	68	5(7.3)	14
India	2008	12	4(33.3)	15
India	2007	326	36(11)	18
India	2007	66	1(1.5)	17
India	2009	211	5(2.4)	16
India	2009	216	7(3.1)	5
Present study	2010	223	45 (20.17)	Present study

DISCUSSION

The present study showed 20.17% of XDR-TB strains amongst a total of 223 MDR- TB strains . The figure being high, it must be emphasized that this was observed in a referral hospital setting.

Data of patients undergoing treatment for MDR-TB in USA showed the presence of XDR-TB as 6.5%, Germany 10.3%, Russia 13.6%, Italy 14.3% and in Hong Kong 12%. Republic of Korea had reported 15.4 % of XDR-TB cases from a total of 1298 MDR-TB strains[9-11]. During 2008, 963 XDR-TB strains were reported to WHO from 33 countries. In January, 2010 also, as many as 58 countries reported XDR-TB strains to WHO.[5]

Previous data from India as observed by unaccredited laboratories showed varying results as 7.3% XDR-TB strains by Mondal *et al* and 33% of XDR-TB strains reported by Singh *et al*, Sharma *et al* reported 2.4% XDR-TB strains and Ramachandra *et al* reported 3.1% XDR-TB strains[4-16,5]**.** The only accredited laboratory TRC Chennai which did population-based survey, reported prevalence of 1.5% XDR-TB[17].

An abstract from Hinduja Hospital, Mumbai presented at American Thoracic Society International Conference held in May 2007 at San Francisco observed that among the total tested 326 MDR-TB strains, 11% were XDR-TB strains[18]. However, these are again hospital-based data and none of these laboratories are accredited, more so for second line drug testing.

Present study showed that MDR-TB is not only resistant to quinolones and aminoglycosides but other second line ATT drugs also.

Kanamycin and capreomycin cross resistance pattern is a common finding ranging from 20% -60% resistance documented in CDC unupdated data and was seen in this study also[19,20].

We observed maximum resistance to ofloxacin 69% [154/223]. This may probably be due to random use of quinolones by many registered and non-registered practitioners for common diseases. This highlights the problem in opting drug regimen to treat MDR cases. Widespread simultaneous usage of many second line ATT drugs for treatment of MDR-TB and fluoroquinolones for treatment of other diseases like upper respiratory tract infection, urinary tract infection, etc., at the same time, in the country may be the reason for the emergence and spread of resistant TB in community. Singh *et al* reported that 7% and 53% of *Mycobacterium tuberculosis* strains were resistant to ofloxacin isolated from category 1 and category II respectively from patients of Kanpur and Agra[21].

Reports from Korea showed 4.4% resistance to fluoroquinolones drug which could be due to lesser usage of the drug in their country[10].

Eighty per cent of the total XDR-TB strains were found to be resistant to three or more second line ATT drugs. Saha *et al* also found that 70% of the total XDR-TB strains were found to be resistant to two or more second line ATT drugs[10]. This may be due to the fact that use of second line ATT drugs is widespread and unchecked.

Despite giving the complete picture of XDR-TB strains, the limitation is that data do not represent the population status. Likelihood of selection bias is there because all the strains were multidrug resistant strains and are not representative sample of the community. This data cannot be generalized for the general population. Some more population-based surveillances can be undertaken. Another limitation of this study is the lack of clinical information of patients because we haven't tracked the record of these patients. Despite these limitations of this study, the existence of XDR-TB in India is well-understood. Its prevention calls for an urgent and rational use of second line Anti-TB drugs and pragmatic management of MDR-TB. Further, more data are required to be generated at the community level.

CONCLUSION

In conclusion, the multidrug resistant TB cases need urgent and timely sensitivity report for second line ATT drugs to help the clinicians start

proper drug combinations to treat MDR-TB patients. More detailed and population-based studies are required to know the burden of XDR-TB strains in community. XDR-TB is throwing an open challenge to clinicians and policy makers as mycobacterium is growing immortal and devastating.

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