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Drug Susceptibility Pattern of *M.Tuberculosis* Isolated from Patients Attending a Private Hospital

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Abstract: Problem statement: Drug resistance in Tuberculosis (TB) is an emerging problem that adversely affects patient outcome and public health in the developing world. Although much of tuberculosis care is provided by the private sector in India, the magnitude of drug resistance in TB in the private sector is not well described. The present study was carried out to determine the resistance pattern of tuberculosis in patients attending a large tertiary care hospital in South India. **Approach:** Anti-tuberculosis resistance patterns of all *Mycobacterium tuberculosis* (*M.tb*) isolates in a tertiary care referral hospital from January 2010 to December 2010 were studied retrospectively. Isolates were grown in MB/BacT automated liquid culture system. Sensitivities to various anti-tuberculosis drugs were done by the proportion method on Lowenstein-Jensen (L-J) media. **Results:** During the study period, sensitivity reports for 50 Mycobacterium isolates were available.14 (28%) of the isolates were multi-drug resistant isolates (resistant to both isoniazid and rifampicin). Isolated resistance to isoniazid, rifampicin, ethambutol, pyrazinamide and streptomycin were 42, 32, 28, 48.28 and 44% respectively. Moxifloxacin was tested against only 12 tuberculosis isolates and was uniformly sensitive against all isolates tested. **Conclusion:** Nearly one third of *M.tb* isolates in a private sector tertiary care hospital were multi-drug resistant. Isolated resistance to ethambutol was the lowest among the first line anti-tuberculosis drugs and resistance to moxifloxacin was not seen in this study. Even allowing for referral bias, our results suggest that tertiary care hospitals which see complicated tuberculosis patients should routinely ask for susceptibility tests whenever *M.tb* is cultured.

Key words: Tuberculosis, Drug resistance, Multidrug-resistance, Private health care

INTRODUCTION

Drug resistant Tuberculosis (TB) is a not a new phenomenon and has been known from the time when drugs were introduced for the treatment of TB. Drug resistant TB adversely affects patient outcome and public health in the developing world. The past two decades have seen the global appearance of Multidrug-Resistant Tuberculosis (MDR-TB) (Frieden *et al*., 1993; Robert *et al*., 2003), followed by Extensively Drug-Resistant Tuberculosis (XDR-TB) (Shah *et al*., 2007) and of late strains those are resistant to all antituberculosis drugs (Velyati *et al*., 2009). Data from the published literature are insufficient to indicate whether the incidence of Multidrug-Resistant (MDR) TB is rising or falling globally as many national programs are failing to diagnose MDR tuberculosis. Globally, only 30, 000 cases of MDR-TB were reported to World Health Organization (WHO) in 2008, compared to the estimate of 440,000 cases (7% of the estimated total). The WHO/IUALTD Global project on Anti-tuberculosis Drug Resistance Surveillance recorded considerable variation in the prevalence of drug resistance among 35 countries in 5 different continents (Velyati *et al*., 2009).

Drug susceptibility testing in India is not routinely performed and public health laboratory infrastructure is limited and poorly equipped to cope with large scale testing. Most of the published reports on tuberculosis drug resistance in India came from surveillance studies conducted in outpatient settings under Revised National TB Control Program (RNTCP) (Paramasivan *et al*., 2002; 2000). However a substantial proportion of patients with tuberculosis or drug resistant tuberculosis seek care with private care providers International Institute of Population Sciences IIPS, 2007. In countries with high burden of MDR tuberculosis, more than half of all sales of first line anti-tuberculosis drugs occur in the private care sector and the proportion is even higher for sales of second-line

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drugs (GATBDD, 2007). The information on anti tuberculosis drug resistance from private health care sector is localized within certain regions of India (Rodrigues *et al*., 2006). The aim of the present study was to describe the pattern of drug resistance among *M.tb* isolates in patients attending a private tertiary care referral hospital in South India.

MATERIALS AND METHODS

This was a retrospective, descriptive, laboratory based study of tuberculosis isolates from the patients attending a 600 bed tertiary care hospital located in Chennai, South India between January 2010 and December 2010.

Isolates were grown in MB/BacT automated liquid culture system. Sensitivities to various anti-tuberculosis drugs were done by the proportion method on Lowenstein-Jensen (L-J) media.

The following definition of resistance was followed in defining the isolates:

- Multidrug-resistance: resistance to both isoniazid (H) and rifampicin (R)
- Monoresistance: resistance to only one drug
- Polyresistance: resistance to two or more drugs excluding HR resistance
- Drug sensitive: absence of resistance to any of the drugs

The ethical committee of the hospital gave ethical clearance for this study.

RESULTS

During the study period, drug susceptibility results were available for 50 of the *M.tb* isolates. Of the 50 isolates 14 (28%) were drug sensitive isolates (susceptible to all the anti-tuberculosis drugs) and 14 were MDR isolates. Poly-resistant isolates were the predominate isolates (15/50-30%) in this study and mono-resistant isolates were seen only in 7 isolates (14%), but none of the isolates were extremely drug resistant (XDR) TB isolates in this study.

As shown in Table 1 among the individual first line drugs the resistance rates were 48.28, 44, 42, 32 and 28% for pyrazinamide, streptomycin, isoniazid, rifampicin and ethambutol respectively. For the second line drugs resistance rate were 32.26% for ethionamide and 17.22% for amilkacin. Moxifloxacin was the only drug sensitive 100% of the time (13/13 of the isolates) in this study.

Table 1: Drug susceptibility patterns of Mycobacterium tuberculosis isolates to first and second line drugs

Drugs (Total no isolates tested)	Sensitive (N)	Resistant (N)	Resistance rate (%)
Isoniazid (50)	29	21	42.00
Rifampicin (50)	34	16	32.00
Pyrazinamide (29)	15	14	48.28
Ethambutol (50)	36	14	28.00
Stretomycin(50)	28	22	44.00
Amikacin (29)	24	5	17.22
Etionamide (37)	21	16	32.26
Moxifloxacin (12)	12	0	0.00

DISCUSSION

Our study found a high prevalence of drug resistance to at least one anti-tuberculosis drug (72%) and an MDR-TB prevalence of 28% in patient attending our tertiary care hospital in South India. The estimated prevalence of MDR-TB in our study was less than in other study conducted in a tertiary hospital in Mumbai (Almedia *et al*., 2003) (resistance to any one drug 80% and MDR-TB 51%). However it was substantially higher than rates found in a number of surveillance studies conducted in RNTCP programs (resistance to any one drug was 21-46% and MDR-TB 2.4-17.4%) (Chandrasekaran *et al*., 1990; Anuradha *et al*., 2006; Ramachandran *et al*., 2009). Bias in the selection and differences in the methodology may explain such variations in the prevalence rates.

The resistance rates noticed in our study to isoniazid and rifampicin were 42 and 32% respectively. Previous surveillance studies conducted in the state of Gujarat (Ramachandran *et al*., 2009) showed that the frequency of INH and rifampicin resistance were in the range of 11-37% for INH and 2.5%-18% for rifampicin and the study conducted by the Deodhar *et al*. (1999) in Bombay showed similar rates to our study (H-30.41%, R- 58.55%). This high rate of INH and rifampicin resistance may be due to wide spread use of these drugs in first line treatment of patients and possibly irregular and inadequate dosing of the drug. In our study, the highest (48.28%) resistance among the first line drugs was found against pyrazinamide. PZA susceptibility testing is not routinely recommended as it acts at a lower pH where bacteria do not grow, but for special reasons it can be performed in small number of isolates (UNION/WHO, 1994; Mitchison, 2005). In our study ethambutol had the lowest resistance rate among the first line anti-TB drugs (28%), similar to previous surveillance studies (1.9-10.2%). This advantage should be exploited while constructing an effective empiric second line regimen for MDR-TB.

Among the second line drugs, ethionamide has got maximum resistance in our study with 32.26%, a

prevalence rate similar to studies conducted in the RNTCP (25-40.5%) (Ramachandran *et al*., 2009). Resistance to ethionamide is difficult to interpret because of technical reasons (Mitchison, 2005). In addition there may be cross-resistance with INH due to a mutation in the inhA gene. Moxifloxacin is the only drug that retained 100% susceptibility in this study; no other studies in India tested this drug. This 100% susceptibility seen in our study could be due to very limited use of this drug in both the private sector and in national programs due to its high cost. Resistance to streptomycin was much higher when compared to amikacin in this study (44 Vs 17.22%). Streptomycin resistance is a concern as it is an essential component of category II DOTS regimen.

Our study has limitations. Clearly there may be a referral bias towards sicker patients and relapses of TB in a referral hospital. Patients' clinical data, drug exposure history and outcomes were not analyzed.

CONCLUSION

In conclusion we found that up to 28% of patients in private settings may have MDR-TB. We recommend routinely doing mycobacterial cultures on clinical samples from all patients with TB and drug-susceptibility testing on all isolates of *M.tb*. There is clearly a need to further study anti-TB drugs resistance in hospital based TB patients from private health care institutions.

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