Original Article

The pattern of anti-tuberculosis drug resistance in pulmonary tuberculosis patients

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Background: Tuberculosis is one of the major public health problems in Nepal.. , Drug resistant tuberculosis has posed a serious challenge in TB control program. Drug resistance tuberculosis is the most difficult for the treatment and cure of the patient.
Objective: To find out the current situation of drug resistant pattern at national tuberculosis center, Nepal.
Design: Central Department of Microbiology, Tribhuvan University in collaboration with NTC, STC, conducted a prospective study.
Methods: One hundred ninety-nine *Mycobacterium tuberculosis* isolated from the sputum in national tuberculosis center (NTC) were studied to find out the drug resistant pattern by utilizing absolute concentration method.
Results: Of the 199 culture positive strains were tested, 161from previously treated cases and 38 from new cases. Overall primary and acquired resistance were 36.82%and 75.05%respectively. The study showed that the Primary drug resistance (PDR) to one drug was found to be 23.67%, to two drugs was 10.52%, to three drugs was 0%, and four drugs was 2.63%where as acquired drug resistance (ADR) to one drug was 32.38%, to two drug was 19.19%, to three drugs was 11.78%, to four drugs was 11.80%. Primary and acquired multi-drug resistance (MDR)) was in 2.63% and 19.25% of the isolates respectively
Conclusion: Overall, drug resistance of *M.tuberculosis* is high. It is concluded that regular monitoring of MDR–TB and making policy according to research finding is necessary as it is changing every year, which helps to control MDR-TB.

Introduction

Drug resistant tuberculosis is one of the serious challenges to global public health. Drug resistant tuberculosis is a case of tuberculosis (usually pulmonary) excreting bacilli resistant to one or more anti-tuberculosis drugs. Resistance of *M. tuberculosis* to anti-tuberculosis drugs is a man made amplification of natural phenomena. Exposure to single drug- due to irregular drug supply, inappropriate prescription or poor adherence to treatment suppress the growth of the susceptible bacilli to that drug but permits the multiplication of drug resistance organism, which is a phenomenon called as acquired resistance. Subsequent transmission of such bacilli to other person may lead to disease, which is drug resistant from the outset, a phenomenon known as primary or initial resistance. MDR-TB is resistant to at least Isoniazid and Rifampicin, the main anti-tuberculosis drugs[1, 2].
Drug resistance poses a major problem, because it is difficult and expensive to treat successfully. It most commonly arise as a result of poor treatment regimens, often because doctors have failed to follow national treatment guidelines[3]. Testing for drug resistance is too expensive for routine use,and is usually restricted to epidemiological surveys and patients who have failed on a Category 1 regimens[4]. The prevalence of drug resistance varies geographically, and is generally higher in technically advanced countries[5, 6].
Directly Observed treatment short course (DOTS) strategy was adopted as policy in1995 in Nepal, introduced in1996

and presently DOTS coverage is more than 95%[7]. The WHO target of 70%case detection was achieved in 2001 and present treatment success rate is 90%[8]**.** There were very few studies, based on different centers, showing different pictures of MDR-TB and no national picture on MDR-TB has been revealed by any such studies. so this study has been planned with the clear cut objective to find out/evaluate the pattern of Anti Tuberculosis Drug Resistance in pulmonary Tuberculosis cases, visiting the National Tuberculosis Centre, a referral hospital for TB treatment.

Methodology

The study was carried out during September 2003 to July 2004 at NTC ,Thimi , Bhaktapur , a referral laboratory for tuberculosis drug sensitivity test. Of the 199 isolates of *M.tuberculosis* obtained from ogawa media were studied .Among them 38 isolates were new cases or from untreated TB patients and 161 isolates from old cases or previously treated TB patients. The isolates culture were confirmed by biochemical tests (Niacin , Nitrate , Catalase , and urease)[9]. Susceptibility testing was done by using absolute concentration method[10]. Tests of Sensitivity to Isoniazid, Rifampicin, Streptomycin and Ethambutol were performed on 1% ogawa media containing drugs on various concentration and 1% ogawa media free of drug was taken as control. The strains were considered resistant to the respective anti- tubercular drug if growth was observed at the following concentration.

Isoniazid -1µg/ml
Rifampicin-50µg/ml

Ethambutol-5µg/ml
Streptomycin-20µg/ml

Results

Out of 199 culture positive isolates, 64 isolates were sensitive to all four anti TB drugs remaining were resistant to at least one drug *(Table 1).*

Table 1 Antibiotic susceptibility pattern among PTB isolates.

S.N.	Drug Susceptibility Testing Result	Untreated TB Patients		Treated TB Patients		Total
		No.	%	No.	%	
1.	Total Tested	38	19.1	161	80.9	199
2.	Sensitive to all 4 Drugs	24	63.2	40	24.8	64
3.	Resistance to 1 Drugs					
	INH	2	5.26	15	9.31	17
	SM	6	15.78	31	19.25	37
	RMP	0	0	5	3.1	5
	EMB	1	2.63	1	0.62	2
4.	Resistance to 2 Drugs					
	INH+ RMP	0	0	2	1.2	2
	INH+ SM	2	5.26	16	9.93	18
	RMP+ SM	0	0	7	4.34	7
	INH+ EMB	1	2.63	3	1.86	4
	SM + EMB	1	2.63	3	1.86	4
5.	Resistance to 3 Drugs					
	INH+ RMP + SM	0	0	8	4.96	8
	RMP+ SM + EMB	0	0	5	3.10	5
	RMP + INH+ EMB	0	0	2	1.24	2
	INH +SM + EMB	0	0	4	2.48	4
6.	Resistance to all 4 Drugs	1	2.63	19	11.8	20
7.	Multi-Drug Resistance (MDR) at least INH + RMP	1	2.63	31	19.25	32

Primary drug resistant cases: The primary drug resistance (PDR) to one drug was 23.67 %(n=9), to two drugs was 10.52 %(n=4), to three drugs was 0 %, to four drugs was 2.63 %(n=1) and primary MDR was in 2.63 %(n=1) of the isolates.
Acquired drug resistant: - Acquired drug resistance to one drug was 32.28 %(n=52), to two drugs was 19.19 %(n=31), to three drugs was 11.78 %(n=19), to four drugs was 11.80 %(n=19) and acquired MDR was in 19.25 % of the isolates.

Table 2 Primary and Acquired anti-tuberculosis drug resistance

Drug resistance	1 Drug	2 Drug	3 Drug	4 Drug	Any Drug	MDR
Primary Drug resistance (n=38)	23.67%	10.52%	0%	2.63%	36.82%	2.63%
Acquired Drug resistance (n=161)	32.28%	19.19%	11.78%	11.80%	75.05%	19.25%

Discussion

This study showed 36.84%isolates were drug resistant in new cases whereas 75.16%isolates were drug resistant in old cases. The level of primary or initial MDR was found to be 2.63% and acquire MDR 19.25% of the isolates. The anti-tuberculosis drug sensitivity test conducted in Nepal during 1987-1990 revealed that 2.8% of the isolates were resistant to RMP, 17.6% to INH and 4% EMB. In this study, initial or primary MDR was 5.7% and acquired MDR was 30% cases respectively[11]. In a similar study conducted in 1991-1994, 0.5% isolates were Rifampicin resistance, 3.2% resistance to INH, 2.5% resistance to EMB. Initial MDR was 1.6% and acquired MDR 9.6% respectively[11]. In study (1994-1997), WHO and IUATLD demonstrated 5.7% of the isolates were mono resistance and 1.1% MDR[12]. The global surveillance data of WHO and IUATLD, 2000 revealed that 4.8% of the initial isolates were mono resistance; initial MDR was 1% and acquired was 7.4%[13].Another study conducted in tertiary care center, Tribhuvan University Teaching Hospital in 2000 demonstrated that mono resistance to untreated cases was 9.8% and initial MDR was 8.6%[14]. Another study conducted in GENETUP, Kalimati, 2003 demonstrated that initial or primary MDR was 4.6% and acquired MDR 5% of the isolates[15]. The latest surveillance report of the IUATLD/WHO, 2004 showed that 1.3% and 20% of untreated (new) and treated (old) cases had MDR-TB in Nepal[16]. Our study findings i.e. percentage of acquired MDR is similar with WHO findings, but percentage of primary MDR is higher than WHO findings. This difference may be due to the limitations of smaller sample size taken from new patients.

This study like other study done in tertiary care, referral hospital has shown relatively high level of drug resistance. Those referral centers where patients were coming from all parts of country and concentrated with relapse, chronic, treatment interrupted treatment failure as well as serious patients for admission. Therefore, those studies conducted in referral center should not be generalized.

It is concluded that regular monitoring of MDR–TB and making policy according to research finding is necessary as it is changing every year, which helps to control MDR-TB.

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