Drug Resistant Pulmonary Tuberculosis among Patients Visiting National Tuberculosis Center, Kathmandu

Ghimire P [a], Rijal KR [a], Rijal B [b] and Bam DS [c]

Abstract

Introduction	Tuberculosis is one of the major public health problems in Nepal. In Nepal, 45 percent of the total population is infected with TB, out of which 60 percent are adults. Every year 40,000 people develop active TB, of whom 20,000 have infectious pulmonary diseases. Drug resistant tuberculosis has posed a serious challenge to TB control program.
Objectives	To determine acquired drug resistance pattern among the treated PTB cases like relapses, chronic, defaulter, treatment failure, etc.
Methods	Central Department of Microbiology, Tribhuvan University in collaboration with NTC, STC, conducted a prospective study during Sept. 2003 till July 2004. During the study period, 325 pulmonary tuberculosis (PTB) patients, attending NTC were included in the study. Out of them 199 isolates were culture positive. Of the 199 culture positive isolates, 161 were from previously treated cases, which were then studied further to find out the drug resistant pattern of treated cases using absolute concentration method.
Results	Out of 325 sputum samples cultured, 61.43 percent (n=199) were culture positive, 32 percent (n=104) were negative and 6.7 percent (n=22) showed contamination. Out of the total culture positive isolates, 74.37 percent (n=148) were from male and 25.63 percent (n=51) were from female patients. Among the culture positive cases, the highest prevalence of PTB observed among the Janjati ethnic group i.e. 47.73 percent (n=95) followed by, Chhetri 22.6 percent (n=45), Newar 15.07 percent (n=30), Brahmin 8.0 percent (n=16), Dalits 3.0 percent (n=6), Muslims 1.0 percent (n=2). Of the total culture positive isolates, 19 percent (n=38) were from the untreated PTB cases while 80.9 percent (n=161) were from the treated PTB cases at different phases of treatment. Out of 161 treated cases 78.88 percent, (n=127) were relapses and 9.33 percent (n=16) were chronic, 6.8 percent (n=11) were follow-up and 1.2 percent (n=2) were treatment failure.
	Highest percentages of MDR (100%) were obtained from the treatment failure cases, though the number of cases was only two; followed by chronic cases (50%) follow up (18.18%) & relapses (14.96%). Primary drug resistance was a strong risk factor for failure and relapse and for acquiring further resistance. As 100 percent of failure cases had MDR, so it is concluded that DOTS plus is necessary for treatment failure cases.
Conclusion	MDR TB among treated cases was about 20 percent and highest in treatment failure followed by chronic (50%), follow up (18%) and relapse (15%).
Key words	Pulmonary tuberculosis, Drug resistance, Relapse, Treatment failure, Ethnic groups

Introduction

Approximately 16 million people in the world are suffering from active tuberculosis, resulting in approximately 2 million deaths each year. Tuberculosis is caused by *Mycobacterium tuberculosis* (and

Corresponding Author : Dr. Prakash Ghimire, E-mail: prakashghimire@yahoo.com, [a]Central Department of Microbiology, Tribhuvan University, Kirtipur, Kathmandu; [b]SAARC TB Center, Thimi, Bhaktapur; [c]National Tuberculosis Center, Thimi, Bhaktapur, Nepal.

occasionally by *M. bovis* and *M. africanum*). These organisms are also known as tubercle bacilli or acid fast bacilli. Pulmonary tuberculosis is the most important form of tuberculosis. Main symptoms are: cough for three weeks or more, fever, loss of appetite, weight loss etc[1]

Treated TB cases are defined as:

Relapse

A patient previously treated for TB who has been declared cured or treatment completed, and is diagnosed with bacteriologically positive (Smear or culture) tuberculosis.

Treatment Failure: A patient who while on treatment, remained smear positive or once more become smear positive at the 5th months or later during the course of treatment or was initially smear-negative before starting treatment and become smear positive after the 2nd month of treatment.

Return after interruption (Defaulter): A patient who completed at least 1 month of treatment and returned after at least 2 months interruption of treatment.

Transfer: A TB patient already registered for treatment in one district that transfers to another district where he/she continues treatment.

Chronic: A patient who remained smear sputum positive after completing a directly observed re-treatment regimen [2]

Drug resistance poses a major problem, because it is difficult and expensive to treat successfully. Such cases commonly arise as a result of poor quality treatment regimens, poor compliance of patients, often because treating physicians have failed to follow national treatment guidelines[3]. The culture and sensitivity testing for drug resistance is expensive for routine use in developing countries, and is usually restricted to epidemiological surveys and patients who have failed on DOTS treatment as Category 1 regimens[4]. The prevalence of drug resistance varies geographically, and is generally higher in technically advanced countries[5, 6].

Methods

The study was carried out during September 2003 to July 2004 at National Tuberculosis Center, Thimi, Bhaktapur, a referral laboratory for tuberculosis drug sensitivity test. Three hundred twenty five sputum samples from referred PTB patients were cultured in 3 percent ogawa media. One hundred ninety nine positive isolates of *M. tuberculosis* obtained from ogawa media were studied .Among them 38 isolates were new cases i.e. from untreated TB patients and 161 isolates from old cases i.e. previously treated TB patients. The culture isolates were confirmed by biochemical tests (Niacin, Nitrate, Catalase, & urease)[7]. Susceptibility testing was done by using absolute concentration method[8] Tests of Sensitivity to Isoniazid, Rifampicin, Streptomycin & Ethambutol were performed on 1 percent ogawa media containing drugs on various concentration and 1 percent 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.

Different ethnic populations were grouped on the basis of HMG Population Monograph[9] as follows;

* Caste Origin Terai Hindu Groups: -

(a) Brahmin: - Maithil, Bhumihar.

(b) Chhetri: - Rajput

(c)Vaisya:- Yadav, Kayastha, Halwaii, Sonar etc.

(d) Sudra:- Bantar, Mushahar, Chamar, Dom etc.

Dalits = Kami, Sarki, Damai, Badi, Gaine etc.

Janajati = Magar, Gurung , Rai, Limbu, Tamang, Lama, Sherpa, Sunwar, Bhote, Raute, Moche, Tham, Dhimel, Satar, etc.

Results

Among the studied 325 cases, 75.69 percent (n=246) were male and 24.30 percent (n=79) were female in the

Table 1: Age distribution of PTB patients visiting NJC

Age Group	Male		Female		Total	
	No.	%	No.	%	No.	%
0-10	2	0.60	0	0.00	2	0.60
11-20	21	6.46	13	4.00	34	10.46
21-30	72	22.15	33	10.15	105	32.30
31-40	50	15.38	17	5.23	67	20.61
41-50	45	13.84	8	2.46	53	16.30
51-60	29	8.92	5	1.53	34	10.46
61-70	19	5.84	0	0.00	19	5.84
71-80	7	2.15	2	0.60	9	2.76
Above 80	1	0.30	1	0.30	2	0.60
Total	246	75.69	79	24.30	325	100

Out of the 199 culture positive isolates, 74.37 percent (n=148) were male and 25.63 percent (n=51) were female. The highest number of culturepositive cases belonged to the age group 21-30(35.67 %), followed 31-40(20.60 %).

Table 2: Age sex distribution of culture positive isolates

Age group	Male		Female		Total	
	No.	%	No.	%	No.	%
11-20	15	7.50	7	3.51	22	11.05
21-30	48	24.12	23	11.55	71	35.67
31-40	27	13.56	14	7.03	41	20.60
41-50	30	15.07	3	1.50	33	16.58
51-60	17	8.50	4	2.00	21	10.55
61-70	8	4.02	0	0	8	4.02
Above 70	3	1.50	0	0	3	1.50
Total	148	74.37	51	25.63	199	100

Table 3: Ethnic group distribution of suspected PTB patients

S N.	Ethnic group	Number of patients	Percentage (%)	Culture Positive Patients	Percentage (%)
1	Caste Origin Hindu Group				
	a. Caste Origin Hill Hindu Groups				
	- Brahmin	47	14.46	16	8.0
	- Chhetri	74	22.76	45	22.6
	- Dalits	12	3.69	6	3.0
	b. Caste Origin-Tarai Hindu Groups*	6	1.8	4	2.01
2	Newar	45	13.84	30	15.07
3	Janajati	135	41.5	95	47.73
4	Muslim	4	1.23	2	1.0
5	Others	2	0.61	1	0.5
Total		325	100	199	

Among the culture positive isolates, the highest prevalence of PTB was in Janajatiethnic group i.e. 47.73 percent (n=95) followed by Chhetri 22.6 percent (n=45), Newar 15.07 percent (n=30), Brahmin 8.0 percent (n=16), Dalits 3.0 percent (n=6) and Muslims 1.0 percent (n=2).

Table 4 : Pattern of resistance according to the history of previous treatment

S.No	Drug Susceptibility Testing Result	Relapse		Chronic		Follow Up		Defaulter		Treatment Failure		Total
		No.	%	No.	%	No.	%	No.	%	No.	%	No (%)
1.	Total Tested	127		16	-	11	-	5		2		161
2.	Sensitive to all 4 Drugs	33	25.9	2	12.5	3	27.3	2	40			40 (25%)
3.	Resistant to one Drugs:											
	INH	13	10.2	1	6.2	1	9.1					
	SM	26	20.4	1	6.2	1	9.4	3	60			
	RMP	5	4.43	0	0	0	0					
	EMB	1	0.78	0	0	0	0					
4.	Resistant to 2 Drugs											
	INH+ RMP	2	1.57	0	0	0	0					
	INH+ SM	14	11.1	1	6.2	1	9.1					121 (75%)
	RMP+ SM	6	4.72	0	0	1	9.1					
	INH+ EMB	3	2.36	0	0	0	0					
	SM + EMB	3	2.36	0	0	0	0					
5.	Resistant to 3 Drugs											
	INH+ RMP + SM	5	3.93	3	18.7	0	0					
	RMP+ SM + EMB	2	1.57	2	12.5	1	9.1					
	RMP + INH+ EMB	0	0	0	0	1	9.1			1	50	
	INH +SM + EMB	2	1.57	1	6.25	1	9.1					
6.	Resistant to all 4 Drugs	12	9.44	5	31.2	1	9.1			1	50	

Out of the 161 treatment received cases 78.88 percent (127) were relapse cases, 9.33 percent (16) were chronic cases, 6.8 percent (11) were follow up cases and 1.2 percent (2) were treatment failure PTB cases. Highest percentage of MDR TB (100%) was observed intreatment failure cases followed by Chronic (50%), follow up (18.18%) and relapse (14.96%).

Study data showed that the drug resistance and the history of previous treatment are significantly related.

Table 5 : Pattern of MDR case distribution

Particulars	Relapse		Chronic		Follow Up		Defaulter		Treatment Failure	
	No.	%	No.	%	No.	%	No.	%	No.	%
Multi-Drug Resistance (MDR) at least INH + RMP	19	14.96	8	50	2	18.18			2	100

Multi-drug resistance (MDR) was observed in 14.96 percent of the isolated from relapse cases, 50percent in chronic cases, 18.18 percent in follow-up patients, however none in Defaulter and 100 percent in isolates from treatment failure cases. Acquired drug resistance was observed in 74.01 percent of relapse isolates, 87.5 percent in isolates of chronic cases, 72.72 percent isolates of follow-up cases, 60 percent isolates of defaulter cases and 100 percent of the isolates of treatment failure cases.

Discussion

This study results showed that only 25 percent of the isolates were sensitive to all four drugs used for treating tuberculosis in Nepal, leaving 75 percent of isolates, as resistant isolates treated cases who were treated partially or fully. The anti-tuberculosis drug sensitivity test conducted in Nepal 1987-1990 revealed that 5.7 percent of new and 30 percent of old cases respectively was having MDR-tuberculosis. Another study in 1991-1994 revealed that 1.6 percent of new and 9.6 percent of old cases respectively had MDR-TB[10]. The surveillance report of the IUATLD/WHO 2000 in Nepal showed that 1 percent and 7.4 percent of the new and old cases had MDR TB in Nepal. The latest third global surveillance report of the IUATLD/WHO 2004 in Nepal showed that 1.3 percent and 20.5 percent of the new and old cases had MDR TB in Nepal[11]. Among 161 culture positive isolates, obtained from the previously treated PTB Patients 127 isolates were from relapse cases, 16 isolates from chronic patients, 11 isolates from follow up patients, 5 isolates from defaulter and 2 isolates from treatment failure cases of PTB. Out of 161 treated cases 31cases ie19.25 percent isolates had MDR TB. Highest percentages of MDR (100%) were obtained from the treatment failure cases followed by chronic cases (50%) follow up (18.18%) & relapses (14.96%). Treatment failure cases remain as a source of infection in the community and may transmit diseases to others with MDR resistant bacilli. Such cases are very dangerous for the community[12]. The finding of our study is similar with other studies in

Madagascar, Chanteau et al., (1997)[13] reported the resistance rate was significantly higher (67%) in failures than in relapses (38%) or return after default patients (37%).

This study like other study was done in a tertiary care; referral hospital has shown relatively high level of acquired drug resistance. In referral centers patients come from all parts of country and concentrated with relapse, chronic, treatment interrupted, treatment failure as well as serious patients for admission. Therefore, the studies conducted in referral center may have higher prevalence than in community based health care settings.

It is concluded that regular monitoring of acquired MDR–TB and revising anti tubercular treatment policy according to the national level representative finding is necessary for MDR TB control, as it is changing every year. High percentage of acquired MDR may be considered as an indication for starting DOTS plus strategy.

References

1.   World Health Organization: *Anti-tuberculosis drug resistance in the world: Prevalence and trends,* Geneva, WHO, 2000.

2.   World Health Organization Report (2003) *Global Tuberculosis Control, Surveillance, Planning, Financing, Communicable Disease.* WHO Geneva.

3.   Uplekar MW and Rangan S Private doctors and Tuberculosis control in India. *Tubercle and Lung Diseases,* 1993; 74: 332-7.

4.   Smith Ian and Sharma Navraj. Epidemiological aspects of Tuberculosis in Nepal. *J Nep Med Association* 1996; 34: 59-65.

5.   Jarallah JS, Elias AK, Al-Hajjaj MS, et.al. High rate of Rifampicin resistance Mycobacterium tuberculosis in the Taif region of Saudi Arabia. *Tubercle Lung Diseases,* 1992; 73: 113-5.

6. Raintawan P, Punnotok J, Chaisuksuwan R and Pransugarit V, Resistance of Mycobacterium tuberculosis to anti-tuberculosis drugs in the central region of Thailand, 1996. *The International Journal of Tuberculosis and Lung disease*.1997: 1(4): 299- 301.

7. Collee JG, Fraser AG, Marmion BP, Simmons A, *Mackie McCartney Practical Medical Microbiology*, *15th* edition, Churchill living stone 1999.

8. Minimum essentials of laboratory procedure for tuberculosis control. JICA, 1986.

9. HMG The Population Monograph of Nepal, National Planning Commission, Central Bureau of Statistics, Nepal 2003.

10. Shrestha B, Nehar A and Breyer U The pattern of Anti-tuberculosis Drug resistance in patients treated at an urban TB clinic in Kathmandu Valley. *The journal of Nepal medical association* TB special, 1996; 34(117):36-40

11. World Health Organization and IUATLD. *Anti-tuberculosis Drug resistance in the world.* Report NO2, 1997-2000.

12. Malla Puspa, Factors associated with treatment failure in TB patients at national tuberculosis center *The Journal of Nepal Medical Association TB special, 1996;* vol 34 (117):41 -6.

13. Chanteau S, Rasolofo V, Ramarokoto H & Rasolonavalona O. Anti-tuberculosis drug resistance in Madagascar in 1994-1995. *The International Journal of Tuberculosis and Lung Diseases*. 1997;1(5): 405-10.