Research Article

Anti-tubercular drug resistance and predictors of relapse pulmonary tuberculosis, Nepal

Timilshina M[1], Lamsal A[*2], Dahal I[1], Thapa B[3], Mandal P K[1], Verma S C[4], Ghimire G R[4]

[1]*Department of Microbiology, St. Xavier's College, Kathmandu, Nepal*
[2]*Department of Genomics, Deerwalk Inc. Kathmandu, Nepal*
[3]*SAARC Tuberculosis and HIV/AIDS Center, Thimi, Bhaktapur, Nepal, Kathmandu Medical College and Teaching Hospital, Kathmandu, Nepal*
[4]*National Tuberculosis Centre, Thimi, Bhaktapur, Nepal*

*Correspondence Info:
Apsana Lamsal,
Associate Genetic Data Analyst,
Deerwalk Inc. Kathmandu, Nepal
E-mail: apsana.lamsal@gmail.com

Abstract

Introduction: Relapse cases of pulmonary tuberculosis (PTB) and drug resistance is increasing in National Tuberculosis Centre (NTC), National Tuberculosis Control Programme, Nepal (NTP) and the predictors of relapse PTB is multi-factorial. Initial drug resistant was found to be associated with high relapse cases, so public awareness for regularity of drug intake is highly recommended. Age, sex, occupation, smoking, alcoholism may be important risk factor for relapse. The study aims to determine the prevalence, anti-tubercular drug resistance and predictors of relapse pulmpnary tuberculosis (PTB) cases.
Materials and methods: Suspected relapse PTB patients were enrolled and microscopy, culture and drug susceptibility testing were done for all culture positive cases.
Result and Conclusion: Result and conclusion: Prevalence of relapse PTB was 45.5% (n=127). *M. tuberculosis* isolates resistant to at least one anti-TB drug were 25.4% (n=31), 35.5% (n=11) were mono resistant and 64.5% (n=20) were poly resistant. Multi-drug resistance were 14% (n=17). The farmer (OR=1.96), who rest at home (OR=1.12), smokers (OR=1.48), alcoholics (OR=1.73) and those who were on irregular drugs (OR=4.10) were at high risk of relapse PTB. Almost half of patients studied had relapse PTB and drug resistance was noteworthy. Close monitoring and follow up, adherence of treatment and risk factors identified should be addressed to reduce relapses and emergence of drug resistance.
Keywords: Relapse tuberculosis, Drug resistant tuberculosis

1. Introduction

Tuberculosis remains one of main public health problems, particularly in developing countries.[1] The impact of tuberculosis (TB) on global health has grasped the international attention after the increase in the number of cases worldwide, including the developed countries. There are approximately 10 million new cases and three million deaths annually throughout the world. More than 90% of the cases occur in developing countries. In1993, TB was declared by the WHO as a global public health emergency.[2]

In Nepal, every year 40,000 people develop active TB, of whom 20,000 have infectious pulmonary TB (PTB). The global target of 85% treatment success has already been achieved due to the expansion of DOTS. However, resistance of *M. tuberculosis* to anti-TB drugs has emerged as a major public health threat.[3]

Relapse of PTB is a patient previously treated for PTB who has been declared cured or treatment completed, and is diagnosed with the bacteriologically positive smear or culture.[4] The cases of relapse in national tuberculosis control program (NTP), Nepal is increasing. This is an important risk factor for development of drug resistance.[5] As drug resistance is common the retreatment outcomes are also inferior in these group.[6] Like relapse, re-infection are also at increased risk of harboring drug resistant TB.[7]

The knowledge of the predictors for recurrence of PTB makes it possible to take measures to ensure treatment success.[8] Tobacco smoking has been established as risk factor for developing PTB.[9] Among the infected persons, incidence of PTB is highest during late adolescence and early adulthood.[10] Several studies have shown an association between smoking and PTB and mortality.[11] A recent meta-analysis also reported that those who had close or very close contact with the smoking household members were nine times more likely to have PTB compared to those who had distant contact.[12] A study has also showed that smokers are three times more likely to experience relapse PTB and five times more likely to die compared to non-smokers.[13] Initial drug resistance, Drug irregularity, smoking and alcoholism were associated with a higher likelihood of relapse. Patients who took irregular treatment were twice more likely to have relapse then adherent patient.[11]

The prevalence of relapse in national tuberculosis centre (NTC), NTP is unknown. The pattern of drug resistance and the risk factors associated with relapse PTB is also not studied. This study aims to determine the prevalence of relapse PTB, anti-TB drug resistance and predictors of relapse PTB under programmatic conditions.

2. Materials and Methods

This study was carried out in a NTC, Thimi, Bhaktapur Nepal. Laboratory works were carried out in a combined laboratory of NTC and SAARC TB and HIV/AIDS Centre (STAC). The center runs DOTS and DOTS plus programme and is a center for executing TB prevention and control activities throughout the country. A total of 285 cases of suspected relapse PTB visiting NTC during March 2011 to May 2012 were enrolled in the study. The patient demographics and predictors of relapse PTB were collected using a questionnaire. All the patients agreed to participate in the study and gave informed consent.

The sputum specimens collected from the cases were initially processed by modified Petroff's method and Zihel Neelsen staining of the sediment was done according to standard operating procedures. Processed specimen was cultured on two slopes of LJ-medium and drug susceptibility test for first line anti-TB drugs was performed by 1% proportion method according to standards.[14] The strains were considered resistant to the respective anti-TB drugs if growth observed were more than 1% in comparison to the control: IHN-0.2 μgm/ml; RFM- 40.0 μgm/ml; SM- 4.0 μgm/ml; and EMB-2.0 μgm/ml. Susceptible strain H$_{37}$Rv strain of known resistance to the drugs tested was used as control in each batch of the test.

All collected data were entered in Statistical Package for Social Sciences version 16.0 (SPSS v.16), double checked was analysed. The categorical data were expressed as frequency and percentage and continuous data were expressed as mean ± SD. The odds ratio was calculated for predictors using the multiple logistic regression analysis. Ethical clearance was taken from institutional review board of Kathmandu Medical College and Teaching Hospital.

3. Result

Two hundred and eighty five cases of suspected relapse PTB were enrolled during the study period. The age ranged from 9-90 years with mean ± SD of 42.41±17.66 years. Male: female ratio was 1.9:1 (186, 65.3% and 99, 34.7% male and female respectively). Among 285 cases, 121 (42.4%) were smear and culture positive, 1 (0.3%) was smear negative and culture positive, 152 (53.3%) were smear and culture negative and 11(3.8%) cultures were contaminated (5, smear positive and 6 smear negative). The relapse PTB was 45.5% (n=127).

Out of 127 relapse PTB patients, culture result was available for 122 as culture results were not available for 5 cases due to contamination. Among 122 culture positive cases, 31 (25.4%) *M. tuberculosis* isolates were resistant to at least one anti-TB drug. Eleven (35.5%) were mono resistant and 20 (64.5%) were poly resistant. INH and SM resistant isolates were 5 (16.1%) and 6 (19.3%) respectively. INH+RFP, INH+SM, INH+RFP+SM, INH+RFP+EMB, INH+SM+EMB and INH+RFP+SM+EMB resistant were 5 (16.1%), 1 (3.2%), 4 (12.9%), 3 (9.6%), 2 (6.4%) and 5 (16.1%), respectively. The multi-drug resistant isolates were 17 (14%).

According to multiple logistic regression analysis, farmer (OR=1.965, 95%CI=0.631-6.122), those who rest at home (OR=1.12, 95%CI=0.33-3.82), smokers (OR=1.48, 95% CI=1.13-1.93), alcoholic (OR=1.73, 95% CI=1.28-2.33) and those who were on irregular drugs (OR=4.10, 95% CI, 2.71-6.19) were more likely to develop relapse PTB (Table).

Table: Predictors for relapse pulmonary tuberculosis

Patient characteristics	Relapse		No relapse		Odd's ratio***	95% CI
	n	%	n	%		
Age, n=279*						
≤15	3	2.3	4	2.6	0.54	0.05-4.95
16-30	42	33.0	49	32.2	0.52	0.18-1.54
31-45	32	25.1	32	21.0	0.52	0.19-1.43
46-60	27	21.2	36	23.6	0.78	0.29-2.05
>60	23	18.1	31	20.3	1.00	
Sex, n=279*						
Male	89	70.0	92	60.5	0.66	0.33-1.32
Female	38	29.9	60	39.4	1.00	
Occupation, n=275**						
Service holder	16	13.0	11	7.2	0.93	0.25- 3.47
Business	24	19.5	21	13.8	0.82	0.26-2.60
Farmer	38	30.8	52	34.2	1.96	0.63-6.12
Rest at home	30	24.3	50	32.8	1.12	0.33-3.82
Student	15	12.1	18	11.8	1.00	
Smoking habit, n=275**						
Yes	65	52.8	55	36.1	1.48	1.13-1.93
No	58	47.1	97	63.8	1.00	
Alcohol habit, n=275**						
Yes	63	51.2	45	29.6	1.73	1.28-2.33
No	60	48.7	107	70.3	1.00	
Drug regularity, n=275**						
Irregular	73	59.3	22	14.4	4.10	2.71-6.19
Regular	50	40.6	130	85.5	1.00	

*6 cases had smear negative and cultures were contaminated and were not included for analysis, **These 6 cases along with 4 other cases who did not respond were not included in the analysis, ***1.00 was used a reference category for multiple logistic regression analysis.

4. Discussion

TB is a global public health problem and the efforts to prevent, control and eliminate will hinder due to emergence of drug resistance and HIV co-infection.[15] The drug resistance in relapse PTB cases is emerging and is also hindering to achieve the global target of treatment success rate (85%). The relapse PTB was 45.5% which was less than study reported earlier (57%).[16]

In this study, relapse was higher in males (n=89, 70%) than female (n=38, 29.9%). Higher cases of relapse were also seen in a study done by Soomro and Quazi, 2009 which reported that 62% were males and 38% were females. This could be explained by the fact that males in the Nepali society are bread earner of the family, smoker, alcoholics, and outgoing than females who are mostly house wife, hence males having higher chances of relapse.[17]

Thirty one (25.4%) *M. tuberculosis* isolates were resistant to at least one anti-TB drug and 91 (74.6%) isolates were sensitive to all four drugs. Similar to our study, Temple *et al*. 2008, had shown that 28.1% *of M. tuberculosis* isolates were resistant to at least one anti-TB drug and 71.9% isolates were sensitive to all four drugs.[16]

Among 31 resistant isolates, 11 (35.5%) were mono resistant and 20 (64.5%) were poly resistant. Combined drug resistant was more prevalent in relapse cases visiting NTC. Most of the Rifampicin resistant cases were also resistant to Isoniazid. Isolated Rifampicin resistance was not observed. Our result was supported by the study conducted by Shah *et al*. 2002.[18] Among 122 culture positive relapse cases, 17 (14%) were MDR. A retrospective study in 2005 from Nepal has shown that MDR among relapse were 14.9%. The study has shown the higher prevalence of MDR-TB than studies conducted elsewhere where the prevalence was 12%.[4,19]

The strong predictor for relapse in this study was irregularity of the anti-TB drugs. Farmers, smokers, alcoholics and those who rest at home also predicted relapse albeit at low level. Age, sex and other occupations did not influence the rate of relapse. Our findings is in accordance with the finding obtained by Thomas *et al*. 2005, in which patients irregular on anti-TB drugs (OR=2.5, 95%CI=1.4-4.6) and smokers (OR=3.1, 95%CI=1.6-6.0) were more likely to have a relapse PTB.[11] The study done by Anyama *et al*. 2007, showed farmers were more likely to have relapse (OR=4.63).[20] Our study is also supported by other studies in which the smokers were likely to develop relapse more than two times than non smokers (OR=2.34, 2.53,).[9,21,22] Similarly,

alcoholism was associated with relapse of TB as shown by others (OR=2.45).[21,22] The study has highlighted for the first time in Nepal the patient behaviors (smoking, alcoholism and anti-drug irregularity) as the important predictors of relapse PTB.

5. Conclusions

The relapse PTB cases are increasing in Nepal and the *M. tuberculosis* isolates are also emerging as MDR-TB further complicating the TB prevention and control efforts. Farmers, cases resting at home, smokers, alcoholics and drug irregularity predicted relapse. The prevention of relapse by addressing the predictors through behavior change and communication will help to sustain the achievement made so far in TB control in Nepal. Continuous monitoring and surveillance of anti-TB drug resistance in relapse cases is also required to fight the anti-TB drug resistance.

Acknowledgements

References

1. Hanif M., Malik S., Dhingra V. K. Acquired drug resistance pattern in tuberculosis cases at the State Tuberculosis Centre, Delhi, India. *Int. J. Tuberc. Lung. Dis* 2009; 13, 74-78.
2. Alfaresi MS., Hag-Ali M. Susceptibility pattern and epidemiology of *Mycobacterium tuberculosis* in United Emirati Hospital. *Open Microbiol. J.* 2010; 4: 1-4.
3. Bhatt CP., Bhatt AB., Shrestha B. Drug resistant cases of tuberculosis in directly observed treatment short course. *J. Nepal Health Res Counc* 2010; 8: 44-47.
4. Bam DS, Ghimire P., Rijal KR., *et al*. Drug resistant pulmonary tuberculosis among patients visiting national tuberculosis centre, Kathmandu. *J. Nepal Health Res. Counc* 2005; 3: 23-28.
5. Johnson J., Kagal A., Bharadwaj R. Factors associated with drug resistance in pulmonary tuberculosis. *Indian J. Chest Dis. Allied Sci.* 2003; 45: 105-109.
6. Dooley KE., Lahlou O., Ghali I., *et al*. Risk factors for tuberculosis treatment failure, default, or relapse and outcomes of retreatment in Morocco. *BMC Public Health* 2011; 11: 140. doi: 10.1186/1471-2458-11-140.
7. Salanipoini FM., Nyirenda TE., Kemp JR., *et al*. Characteristics, management and outcome of patients with recurrent tuberculosis under routine programme conditions in Malawi. *Int. J. Tuberc. Lung Dis* 2003; 7: 948-952.
8. Picon PD., Bassanesi SL., Caramori ML., *et al*. Risk factors for recurrence of tuberculosis. *J. Bras. Pneumol* 2007; 33: 572-578.
9. d'Arc Lyra Batista J., de Albuquerque M de Fatima P., de Alencar Ximenes RA., *et al*. Smoking increases the risk of relapse after successful tuberculosis treatment. *Int. J. Epidemiol*. 2008; 37: 841-851.
10. Raviglione MC, Brien RJ. Tuberculosis. In: Fauci AS Braunwald E, Kasper DL, Hauser SI, Longo DL, Jameson JL, Loscalzo J. eds. Harrison's Principles of Internal medicine. Volume 1, [7th] ed, New York, USA: Mcgraw-Hill Companies Inc. 2008: pp 1006-1020.
11. Thomas A., Gopi PG., Santha T., *et al*. Predictors of relapse among pulmonary tuberculosis patients treated in a DOTS programme in South *India. Int. J. Tuberc. Lung Dis* 2005*;* 9: 556-561.
12. Hsien-Ho L., Ezzati M., Murray M. Tobacco Smoke, indoor air pollution and tuberculosis: a systematic review and meta-analysis. *PLoS Med*. 2007; 4, e20.
13. Pradeepkumar AS., Thankappan KR., Nichter M. Smoking among tuberculosis patients in Kerala, India: proactive cessation efforts are urgently needed. *Int. J. Tuberc. Lung Dis*. 2008; 12, 1139-1145.
14. Ministry of Health and Family Welfare, Government of India. Standard Operating Procedures (SOPs) 2006: Intermediate Reference Laboratory for Tuberculosis, New Delhi, India: Ministry of Health and Family Welfare, Government of India.
15. World Health Organization. Global Tuberculosis Control: epidemiology, strategy, financing, WHO report, WHO/HTM/TB/2009.411. 2009; Geneva, Switzerland: WHO.
16. Temple B., Ayakaka I., Ogwang S., *et al*. Rate and amplification of drug resistance among previously-treated patients with tuberculosis in Kampala, Uganda. *Clin. Infect. Dis* 2008; 47, 1126–1134.
17. Soomro JA., Qazi HA., Factors Associated with relapsed tuberculosis in males and females: a comparative study. *Tanaffos*. 2009; 8, 22-27.
18. Shah AR., Agarwal SK., Shah KV. Study of drug resistance in previously treated tuberculosis patients in Gujarat, India. *Int. J. Tuberc. Lung Dis.* 2002; 6, 1098–1101.
19. Abate G., Miorner H., Ahmed O., *et al*. Drug resistance in *Mycobacterium tuberculosis* strains isolated from re treatment cases of pulmonary tuberculosis in Ethiopia: susceptibility to first-line and alternative drugs. *Int. J. Tuberc. Lung Dis*. 1998; 2,580-584.
20. Anyama N., Sseguya S., Okwera A., *et al*. The challenge of re-treatment pulmonary tuberculosis at two teaching and referral hospitals in Uganda. *Afr Health Sci*. 2007; 7, 136-142.
21. Wang J., Shen H. Review of cigarette smoking and tuberculosis in China: intervention is needed for smoking cessation among tuberculosis patients. *BMC Public Health* 2009; 9, 292. doi:10.1186/1471-2458-9-292.
22. Millet JP, Orcau A., de Olalla PG., *et al*. Tuberculosis recurrence and its associated risk factors among successfully treated patients. *J Epidemiol Community Health*. 2009; 63, 799-804.