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Original Article

Clinical spectrum of patients presenting with bronchiectasis in Nepal: Evidence of linkage between tuberculosis, tobacco smoking and toxic exposure to biomass smoke

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Abstract

Aims and objectives: The aim of the study was to describe the clinical spectrum of the patients presenting with bronchiectasis at the referral clinic for the respiratory diseases in eastern Nepal. An attempt would also be made to provide an overview of factors responsible for poor lung health in the community.

Materials and methods: This is a retrospective observational study conducted at the Adult Chest Clinic of the Department of Internal Medicine at the B.P Koirala Institute of Health Sciences (BPKIHS), Dharan Nepal. The medical records of all the consecutive patients presenting with the diagnosis of bronchiectasis in the Adult Chest Clinic of Department of Medicine from January 2003 to December 2004 (two years) were reviewed for patient characteristics (age, gender, place of residence, occupation, smoking history, exposure to indoor air pollution due to use of biomass smoke, past and family history related to tuberculosis, and clinical characteristics such as clinical features and duration of symptoms

Results: During the study period of two years, 100 patients presented with the diagnosis of bronchiectasis, 80 (80%) patients were smokers and 50 (50%) patients had history of significant exposure to indoor air pollution. Abnormal Chest X-ray was seen in 85(85%) patients. Post tubercular bronchiectasis was the most common etiological diagnosis Smoking status and exposure to indoor air pollution were important determinant for hospitalisation in patients with post tubercular bronchiectasis.

Conclusions: In Nepal bronchiectasis remains one of the important chronic respiratory diseases, post tubercular variety being the commonest type .Tuberculosis, tobacco smoking and exposure to indoor air pollution contributes towards higher morbidity of this diseases.

Key words: Bronchieactasis, Indoor air pollution, Lung health, Tobacco smoking, Tuberculosis

Bronchiectasis is defined as the permanent dilatation of one or more bronchi[1]. In clinical practice, it occurs as a clinical syndrome with classical triad of productive cough, purulent sputum and repeated episodes of chest infections. The prevalence of this disease has declined in the developed countries because of early immunization, widespread use of antibiotics in management of childhood respiratory infections, and effective control of tuberculosis [2, 3] In developing countries, it is the third most common diagnosis made in adult patients attending the chest clinics of the large hospitals[4].The literature regarding clinician's view and approaches to bronchiectasis in Nepal is lacking. Current clinical practices are based predominantly on published guidelines from developing countries; and it is unclear how these information are synthesized and applied by the general physicians who are primarily responsible for the care of the patients presenting with chronic cough.We conducted the present study to provide information regarding the clinical epidemiology and the risk stratification of the patients presenting with bronchiectasis in a tertiary care hospital in eastern Nepal

Aims and objectives

The aim of the study was to describe the clinical spectrum of the patients presenting with bronchiectasis at the referral clinic for the respiratory diseases in eastern Nepal

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Materials and methods

This is a retrospective observational study conducted at the Adult chest clinic of the department of internal medicine at the B.P Koirala Institute of Health Sciences (BPKIHS), which is a large 650-bedded university teaching hospital in the eastern Nepal. Adult chest clinic is a special clinical service in the department of internal medicine at BPKIHS which provides comprehensive care to the patients with respiratory diseases. The medical records of all the consecutive patients presenting with the diagnosis of bronchiectasis in the adult chest clinic of department of medicine from January 2003 to December 2004 (two years) were reviewed for patient characteristics (age, gender, place of residence, occupation, smoking history, exposure to indoor air pollution due to use of biomass smoke,past and family history related to tuberculosis, and clinical characteristics such as clinical features and duration of symptoms, and associated co-morbidity). Smoking history was categorized as smokers and non-smokers. Since it is a routine practice at our centre to ascertain the exposure to indoor air pollution by questions relating to the use of type of fuels, exposure to indoor air pollution due to use of biomass smoke was ascertained indirectly from the information in medical records answering question on the type of fuels used by households for cooking and amount of time spent by the person in the kitchen per day. Patients were then categorised into four groups: (i) smokers with exposure to indoor air pollution, (ii) smokers without exposure to indoor air pollution, (iii) non-smokers with exposure to indoor air pollution and (iv) non-smokers without any exposure to indoor air pollution. Chest x-ray findings, reports of sputum examination, CT chest and bronchoscopy were also noted. For the purpose of clinical care bronchiectasis was defined as a distinct clinical entity with the history of chronic cough with purulent sputum and chest x-ray suggestive for bronchiectatic changes [3, 4]. The diagnoses were categorized as follows; (i)A diagnostic level of post tubercular bronchiectasis was given when there was a definite past history of treated pulmonary tuberculosis and radiological picture suggestive of broncheactatic changes and patient presented with persistent cough with muco purulent sputum which was persistently negative for mycobacterium[4] (ii)A patient was diagnosed as having active pulmonary tuberculosis if his sputum examination or broncho alveolar lavage fluid (BAL) yielded tubercle bacilli, or if clinical picture and chest x-ray were suggestive enough in clinicians opinion to initiate empirical anti tuberculosis treatment[5]. (iii)Allergic broncho pulmonary aspergillosis(ABPA) was diagnosed when a patient had productive cough and history of wheezing with peripheral eosinophilia accompanied by fleeting pulmonary in filtrates[4]. The final diagnosis was based on the combination of all clinical, radiological, microbiological, CT and bronchoscopic findings. The study protocol was approved by the institutional ethical review board.

For the statistical analysis Microsoft Windows based statistical package for social sciences (SPSS, version 13) was employed. After analyzing the descriptive statistics, patients were compared based on their primary diagnosis and other variables like age, gender, smoking status, exposure to indoor air pollution, clinical symptoms and their duration.

Results

Patient characteristics

During the study period of two years, 100 patients presented with the diagnosis of bronchiectasis at our study centre. Among them 70 (70 %) were males and 30(30%) were females (with an average age 48.3 years and an age range 16-80 years (std. dev. 16.4)

The characteristics of the study population are summarized in the table (1). 80 (80%) patients were smokers and 50 (50%) patients had history of significant exposure to indoor air pollution due to use of biomass fuels. Majority of these patients belonged to hilly districts of eastern Nepal. Past history of tuberculosis and family history of tuberculosis was present in 64(64%) and 45(45. %) of the patients respectively.

Clinical presentation

Symptoms

Cough with productive and purulent sputum was seen in all the 100 patients presenting with bronchiectasis. Seventy five (75%) patients presented with hemoptysis and majority among them had moderate hemoptysis. Seventy (70%) of the patients also had complaints of progressively worsening shortness of the breath with significant exercise limitations .This symptom was more prevalent among women as compared to men. Half (50%) of the patients had presented with fever and another 50 (50%) of the patients complained of bilateral leg swelling. All these symptoms were seen in isolation as well as in combination. The duration of symptoms ranged from 1 months to more than one year, majority of patients having repeated episodes of recurrent symptoms for prolonged period of time. Among the patients presenting with bronchiectasis, smokers with exposure to indoor air pollution had more severe symptoms, lasting for prolonged period.

Signs

Seventy five(75%) of the patients had abnormal findings in the physical examination of the chest, there were variable combination of coarse crepitations and

wheezes on the affected side. Gross digital clubbing was seen in 75(75%) of the patients. Clinical features of pulmonary arterial hypertention and cor pulmonale was seen in 50(50%) of the patients.Evidence of malnutrition and gross weight loss was seen in 50(50%) of the patients. Clinical features of the study population are summarised in Table 2.

Investigations

Sputum examination was done in all the patients of whom no organisms could be isolated in 50% of the cases. In the remaining, 15 (15%) were positive for mycobacterium tuberculosis. Chest X-ray was performed in all the 100 patients that presented with the bronchieactasis and was found abnormal in 85(85%) patients. Thirty five (35%) of the patients had unilateral diseases with predominant involvement of left side especially left lower lobe, while 20 (20%) of the patients had bilateral disease as evident by bilaterally fibrosed, shrunken and bronchiectatic lung (Table 4 and 5). Computed tomography of the chest was done in 25 (25 %) of the patients. Bronchoscopy was performed more often than CT chest, counting for 30 (30 %). Bronchoscopy revealed extensive distortion of tracheobronchial tree with prominent ulcerations. In majority of cases, the tracheobronchieal trees were filled with profuse and purulent secretions. Pulmonary function test showed mixed patterns of obstructions. Patients had a restrictive pattern of ventilator dysfunction with varying degrees of obstructive changes.

Aetiology of Bronchiectasis

Post tubercular bronchiectasis was the most common etiological diagnosis accounting for 65% of the cases. Twelve (12%) patients had a history of repeated episodes of chest infection in early childhood and adolescence, the patients in this category were young, non smokers, without any past and family history of pulmonary tuberculosis, and presented with symptoms of cough with sputum production of varied duration without any hemoptysis. In 6(6%) of the patients the bronchiectasis was diagnosed due to Allergic bronchopulmonary aspergillossis(ABPA) Raheumatoid arthirits also accounted for bronchiectasis in 6(6%) of the patients all of them were females .Sarcoidosis and repeated episodes of aspiration pneumonitis were less common causes of bronchieactasis in our study population. No specific diagnosis of bronchiectasis could be identified in 5(5%) of patients (Table 6).

Clinical course

Sixty five (65%) of the patients were treated on outpatient basis at regular visits, while 35(35%) of the patients required hospitalisation because of their symptoms. All of the hospitalised patients had post tubercular bronchiectasis, 45% were male current smokers with moderate hremoptysis while 55% were female current smokers with significant exposure to indoor air pollution, and presenting with worsening cor pulmonale

Table 1: Baseline characteristics of the study population

(Total number of patients n=100)	
Patient Characteristics	**Number (%)**
Age & gender	
16 to 40 years	10 (10%)
41-65 yrs	35(35%)
>65 years	55(55%)
Age range	16-85 yrs
Mean Age	48.32 yrs
Male	70(70%)
Female	30(30.)
History of smoking & exposure to indoor air pollution due to use of biomass smoke	
Smokers with exposure to indoor air pollution	45(45%)
Smokers without exposure to indoor air pollution	35(35%)
Non-smokers with exposure to indoor air pollution	5 (5%)
Non-smokers without exposure to indoor air pollution	15(15%)
Family history of Tuberculosis	
Present	45(45%)
Absent	55(55%)
Past history of Tuberculosis	
Present	64(64%)
Absent	36 (36%)
Duration of Symptoms in months:	
1 -3 months	26(26%)
4-6 months	20(20%)
6 months to 12 months	14(14%)
More than 12 months	50(50%)

Table 2: Clinical features of patients presenting with Bronchieactasis

Symptoms	***Number of patients (%)***
Cough with productive & purulent sputum	100 (100%)
Hemoptysis	75(75%)
Shortness of Breath & exercise limitation	70(70%)
Pedal edema	50(50%)
Fever	30(30%)

Si*gns*	***Number of patients (%)***
Clubbing	75(75%)
Abnormal chest finding	75 (75%)
Weight loss	30(30%)
Features of cor pulmonale	50 (50%)

Table 3: Bacteriological isolates in sputum and /or BAL in patients with Bronchiectasis

Organisms	*Number of patients (%)*
No organisms isolated	50(50%)
Mixed flora	20(20%)
Mycobacterium tuberculosis	15 (15%)
Haemophilus influenzae	5(5%)
Staphylococcus Aureus	5(5%)
Streptococcus pneumoniae	3 (3%)
Pseudomonas	2(2%)

Table 4: Diagnostic modalities employed in the evaluation of patients presenting with Broncheactasis

Diagnostic procedure	***Performed**	****Positive Results**
Chest Xray	100/100 (100%)	85/100/(85%)
CECTchest	25/100(25%)	25/25(100%)
Bronchoscopy	30/100(30%)	30/30(100%)

*The diagnostic modalities performed are displayed as absolute numbers and as (%) of the total numbers of patients included in the study.

**A positive result signifies the contribution of that investigative modality in making the diagnosis in absolute number and (%) percentage

Table 5: Chest x-ray features of Bronchiectasis

Chest x-ray findings	*Number of patients (%)*
Unilateral disease(left lower lobe predominant)	35(35%)
Bilaterally destroyed lung (fibrosed, shrunken & broncheactatic changes in bilateral lung field)	20(20%)

Table 6: Aetiology of Bronchiectasis

Etiology	*Number of patients (%)*
Post Tubercular Broncheactasis	65(65%)
Recurrent chest infection in early childhood & adolescence	12(12%)
Allergic bronchopulmonary aspergillosis (ABPA)	6 (6%)
Rheumatoid arthritis	6(6%)
Sarcoidosis	3(3%)
Aspiration pneumonitis	3 (3%)
No specific diagnosis	5(5%)

Discussion

We have described contemporary clinical presentation and demographics of patients presenting with bronchiectasis, diagnosed by clinical history and appropriate radiological investigation, at clinical service specially devoted for the care of patients with respiratory disease at a large tertiary care hospital in a developing country.

In our study, more males presented with bronchiectasis than females. Most of the patients had typical clinical manifestations including persistent cough, increasing sputum production and hemoptysis. Similar findings have been reported from various other studies[6,7]. Majority of our patients presented with mild to moderate hemoptysis, consistent with findings reported in literature that bronchiectasis being the most common cause for recurrent hemoptysis [8]. One of the striking finding in our study was higher percentage of patients presenting with shortness of breath and features suggestive of cor pulmonale. Other studies have also reported the evidence of airway obstruction in cases of bronchiectasis, causing significant dyspnoea even in patients with localized diseases and extensive bronchiectasis often leading to chronic cor pulmonale[9,10].

The diagnosis and assessment of bronchiectasis might have become relatively easy, with the advent of computed tomography[2]; but we found Chest x-ray an important tool for investigation of bronchiectasis in resource poor settings because a normal chest x-ray virtually ruled out its possibility in patients who presented with characteristic symptoms in our study. Therefore, investigating a patient in resource poor settings, we suggest that chest radiograph should be employed as the next investigating tool after targeted history and clinical examination. The cost and availability of HRCT chest is a limiting factor to employ this modality of investigation routinely. Moreover the radiographic and pathological classification of bronchiectasis into cylindrical, cystic varicose variety does not add significantly towards determining etiology, treatment or prognosis in individual patients[11].

Surprisingly, most patients in our study group had no growth of organisms in sputum culture, this might be because of the fact they were treated with multiple course of antibiotics over the prolonged period of time, before being referred to our center. This is in contrast with the study conducted by Angrill et al where they reported 64% incidence of colonization with potentially pathogenic microorganisms from the sputum of stable patients with bronchiectasis, H. influenzae and pseudomonas species being the most common[12]. Since, mixed infections are commonly seen in sputum of patients of bronchiectasis, it is often unnecessary to perform sputum culture and sensitivity tests with each episode of exacerbation of bronchiectasis, thus the empirical use of antibiotics is justified[13]. An important finding in our study was presence of active tuberculosis in 12% of the patients as evident by presence of mycobacterium tuberculosis in the sputum[14]. Half of the patients with active tuberculosis were chronic alcoholics, one third had diabetes mellitus, and remaining of them were current smokers having extensive exposure to indoor air pollution of biomass fuels.

Pulmonary function test showed mixed patterns of obstructions in majority of the cases. Patients had a restrictive pattern of ventilator dysfunction with varying degrees of obstructive changes. Functional impairment in bronchiectasis is related to the extent of lung damage, as determined by numbers of bronchopulmonary segments involved, presence of bronchial infection and associated changes in lung parenchyma are the major determinants of pulmonary dysfunctions[15].

The past and family histories of tuberculosis were very helpful in predicting the etiology of bronchiectasis in our study. Post tubercular broncheactasis was the most common etiology identified .Post tubercular bronchiectasis occurs when post primary pulmonary tuberculosis, after specific therapy, leaves behind distorted and dilated bronchi in the affected lobes which lead to continuation of respiratory symptoms, especially hemoptysis, even after long eradication of mycobacteria[4]. Sometimes healed tuberculosis or traction on major airways from surrounding lung parenchyma, disrupting their architecture can cause this entity[14]. These patients are symptomatic with recurrent bouts of bronchial infection and show gross bronchiectatic changes in chest x-ray. In our study population, post tubercular bronchiectasis was the most likely diagnosis in middle aged patients (41-65 years), with past history of tuberculosis, who present with moderate to severe hemoptysis along with productive cough and shortness of breath .Results of our finding also coincide with recent other series from developing countries which mentions post tubercular bronchiectasis as an important cause of bronchiectasis. Stephen & Rajasekharan et al from a study in India also reported post tubercular bronchiectasis as the commonest cause of bronchiectasis[14, 15, 16]. .Similar findings have also been reported from various studies from other parts of the world. This shows that in spite of effective tuberculosis control programs, pulmonary tuberculosis and its sequels are still important causes of chronic respiratory diseases in the developing countries[14, 15].

Recurrent childhood respiratory infection was identified as a cause of bronchiectasis in nearly 12% of the

patients; these were young, non smokers, without any past and family history of pulmonary tuberculosis and presenting with non specific respiratory symptoms of varied duration. Similar to other series a substantial number of our patients had recurrent infection in early childhood and adolescence, which emphasizes the importance of effective treatment of childhood respiratory infections[17, 18, and 19].

About 6% of the patients presenting with bronchiectasis had ABPA. These patients had mainly upper lobe bronchieactasis with past history suggestive of chronic atopy and asthma. ABPA occurs in asthmatics and atopic persons accounting for about 10% cases of bronchiectasis[4, 6]. It is important to identify this condition as the predisposing factor for bronchieactasis because treatment with corticosteroids significantly improves the lung function in this subgroup of patients[20]. No etiology was found for bronchiectasis in 2% of the cases in our study. This percentage however was smaller than that reported by other series. These patients had generally good health, without any obvious risk factors for respiratory diseases and had normal chest x-ray. Theoretically it is possible to have idiopathic bronchiectasis of undetermined pulmonary pathology in a fraction of patients.

Some unifying theme emerges from the findings of our study. The findings reflect upon the increasing trend of tobacco smoking and presence of other risk factors associated with chronic lung diseases in the local community, specially the patterns of house hold energy use and extent of indoor air pollution in the population. The prevalence of smoking has been gradually increasing in developing countries over the last decade In Nepal, 33.7% of the urban population and 46.35 of rural population smokes tobacco[21]. In developing countries almost 85% of the total energy needs are met by traditional biomass fuels in the rural and semi urban areas. Indoor air pollution has been considered an important factor contributing towards poor lung health especially in people who live in rural areas, small cities, and per urban areas of large cities in the Asian subcontinent[22]. A consistent body of evidence, particularly from China and India, has shown that people exposed to smoking from use of biomass fuel for prolonged period of time have elevated risk of developing chronic respiratory diseases[23, 24].

Our study is unique because we categorized the risk factors associated with smoking and indoor air pollution and examined their relationship with the clinical presentation of bronchiectasis .To the best of our knowledge, this is the first study of this kind.The most striking finding in our study was high incidence of hospitalization in patients of post tubercular bronchiectasis who were current smokers and exposed to indoor air pollutions, they also had reactivation of pulmonary tuberculosis .There is a consistent body of literature indicating that exposure to respirable pollutants from combustion of tobacco and biomass fuels increases the risk of tuberculosis infection[25,26,27,28]. Chronic exposure to tobacco, as well as indoor air pollution from biomass smoke impairs the lung defense mechanism by its effect on mucocilliary function of tracheobronchial mucosa[29], impairs the function of pulmonary alveolar macrophages[29] and impairs the intracellular killing of microorganism by decreased production of TNF alpha[30]. Available data also suggest that smoking and exposure to indoor air pollution may induce progression of tuberculosis or reactivation of tuberculosis[31.32, 33].

The greatest strength of present study is that our institution is both primary and tertiary care hospital, and we believe that spectrum of these patients presenting with bronchiectasis generally parallels the prevalence of chronic lung diseases in the community .It can be taken as the surrogate marker of state of lung health in the community .Despite the well recognized methodological limitation of indirect assessment of indoor air pollution, and possible misclassification of Chronic obstructive pulmonary diseases (COPD) as bronchieactasis, our study gives important information, the implications of our findings for lung health are critical. There is substantial tobacco smoking in Nepal; and tuberculosis is still rampant, and energy needs are met by traditional biomass fuels. Considerable portion of poor lung health can be attributable to these factors, moreover this association implies that smoking cessation, and change in the national energy policy might help in improving the lung health.

In summary, we conclude that in Nepal bronchiectasis remains one of the common chronic respiratory diseases causing significant economic burden, tuberculosis, tobacco smoking and toxic exposure to biomass smoke contribute towards higher morbidity of this disease. A substantial improvement in lung health can be achieved by focusing on intervention aimed at decreasing the tobacco smoking, tuberculosis control and preventing the toxic exposure to biomass smoke. It is, however, a big challenge to everyone involve in managing chronic respiratory diseases-individual patients, clinicians caring for them, professional organizations, health care delivery system, and national health policy makers.

References

1. Seaton D: Bronchiectasis. In Seaton A, Seaton D, editors. Crofton and Douglas respiratory diseases. 5th ed. Volume I. New Delhi: Oxford University Press; 2000.794-808.
2. Barker A .Bronchiectasis .N Engl J Med. 2002; 346; 1385-93.
3. Kiestenin T.O., SynajakangeseT, Tuponnen et al. Bronchieactasis: An orphan disease with poorly understood prognosis. Eur Respir J.1997; 10: 2784-.7.
4. Pande JN: Broncheactasis .In Pande JN (editor). Respiratory medicine in the tropics. New Delhi: Oxford University Press; 1998.259-. 64.
5. Kralingen KW, Kralingen V, Heijboer AC, Zimmerman M, Postmus PE. Management of hemoptysis in the third world hospital: A retrospective study. Tubercle Lung Diseases.1995; 76:344-8.
6. Pasteur CM, Helliwel MS, Houghten JS, et al. An investigation into the causative factor in patients with broncheactasis . Am J Respi.Crit Care Med. 2000; 162:1277-.84.
7. Smith JA Jarrison FD, Edenric S et al . Chronic sputum production, correlation between clinical features and findings on high resolution computed tomography of the chest Thorax.1996; 51 :914-.8.
8. Fidan A, Ozdogan S, Oruc O et al . Hemoptysis; A retrospective analysis of 108 cases. Respir Med.2002;96:677-80.
9. Jain NK Gupta KN, Sharma TN, GargVK, Agnihotri SP. Airway obstruction in in bronchiectasis and its reversibility: study of 38 patients. Indian J Chest Dis Allied Sci.1992;34:7-10.
10. Murphy MB Reen DJ Fitzgard MX, Atopy. Immunological changes and respiratory function in bronchiectasis.Thorax.1984;39:179-84.
11. Reiff D, wells A, Corr D et Al: CT finding in broncheactasis limited value in distinguishing between individual and specific types. Am J. Roentogenol. 1995;165:261-7.
12. Angrill J, Augustin C, de Cellis R et al. Bacterial colonizationin patients with bronchiectasis :Microbial pattern and risk factors. Thorax. 2002;57:15-9.
13. Rosen JM :Chronic cough due to bronchieactasis :ACCP evidence based clinical practice guidelines Chest. 2006: 129: 122-31.
14. Desai S Wells A Ruben Met al traction bronchieactasis in cryptogenic fibrosing alveolitis,associated computed tomographic features and physiological significance Eur Radiol. 2003; 13,1801-8.
15. Rajasekharan S, Bhanushre R, VallanayagiV, Gopal V Nirmaladevi S, value of high resolution computed tomography in diagnosis and assessment of bronchiectasis Ind J Tub. 1997,44,129.
16. Stephen T, Roy T, Madhu PA, Neelakantan N et al: Surgical results in bronchiectasis: analysis of 149 patients. Asian Cardiovasc Thorac Ann. 2007;15:290-6.
17. Kutlay H, Cangir AK, Enon S, Sahin E, Akal M, Gungor A, et al. Surgical treatment in bronchiectasis : Analysis of 166 Patients. Eur J cardiothoracic Surg. 2002 ; 21: 634-7.
18. Agasthanian T, Deschamps C, Trastek VF,Allen MS et al Surgical Management of Bronchiectasis. Ann Thoracic Surg. 1996: 62: 976-80.
19. Annest LS, Kratz JM,Crawford FA Jr. Current results of treatment of bronchiectasis. J Thorac cardivasc Surg 1982: 83: 546-50.
20. Mahasharmani MG, Koziel H. Chronic lung sepsis: lung abscess Brochiectasis & Empyema .Curr Opin Pulm Med.2003;9:181-5.
21. WHO. A study on the economics of Tobacco in Nepal. Kanki YB, pant KD, Pande BR. Nepal (cited 2003 Oct 1). available from: http://repositories.cdlib.org/tc/whotcp/NEPAL2003.
22. Smith KR. Indoor air pollution in developing countries: Recommendation for research. Indoor air. 2002; 12:1-7.
23. Zhau Y, Wang S, Aunan K, Seip MH, et al .Air pollution and lung cancer risk in China –a meta analysis. Science of the total environment. 2006;366:500-13.
24. Gupta D, Bofetta P, Gaborieau V, et al. Risk factors for lung cancer in Chandigarh, India. Indian J Med Res. 2001;113:142-50.
25. Gupta D, Agrawal, AN, Kumar, Jindal SK. Smoking increases the risk of Pulmonary tuberculosis. J Environ Med .2001;3:65-70.
26. Alcaide J, Altet MN, Plans P, Parron I, Folguera, et al. Cigarette smoking as a risk factor for tuberculosis in young adults : a case control study. Tuber Lung Dis. 1996 ;77:112-6.
27. Ariyothi N, Podhipak A, AkarasewiP, Tornee S, Simthkaren S et al. Cigarette smoking and its relationship to pulmonary tuberculosis in adults. South East Asian J Trop Med Public Health. 2004;35:219-27.
28. Leung CC, Li T, LamTH, Yew WW, Law WS et al. Smoking and tuberculosis among elderly in Hong Kong. Am J Respir Crit Care Med. 2003; 170:1027-33.

29. Houtemeyers E, Gosselink R, Gayan R, et al. Regulation of mucocilliary clearance in health and disease .Eur Respir J. 1999;13.177-88.
30. Sopori M .Effect of cigarette smoke in immune system .Nat Rev Immunol. 2002; 2(5):372-7
31. Mishra VK, Rutherford RD, Smith KR. Biomass cooking fuels and prevalence of tuberculosis in India .Int J Inf Dis.1999; 3:119-29.
32. Perez-padilla R, Perez-Gunzman C, et al: Cooking with biomass stoves and tuberculosis: a case control Study. Int J Tuberc Lung Dis. 2001; 441-7.
33. Lin HH, Ezzati M, Murray M. Tobacco smoke,indoor air pollution and tuberculosis; a systematic review and metaanlysis. PLos Med. 2007;4 (1): e 20doi: 10.371/journal. pmed.0040020.