ORIGINAL ARTICLE

ROLE OF FIBER-OPTIC BRONCHOSCOPY IN SPUTUM SMEAR NEGATIVE PULMONARY TUBERCULOSIS

Dimple Kumar Bhaglani[1], Malay Sarkar[2], Digvijay Singh[3], Rameshwar S Negi[4], Sunil Sharma[5]

Author's Affiliations: [1]Junior Resident; [2]Professor & Head; [4]Associate Professor; [5]Assistant Professor, Department of Pulmonary Medicine; [3]Professor, Department of Microbiology, IGMC Shimla, Himachal Pradesh, India
Correspondence: Dr Dimple Kumar Bhaglani Email: d.kbhaglani@gmail.com

ABSTRACT

Objective: To evaluate the utility of fiberoptic bronchoscopy in sputum smear negative PTB patients.

Material and Methods: A total of 66 adult patients with sputum smear negative for Acid Fast Bacilli (AFB) and chest X-ray suggestive of pulmonary tuberculosis underwent fiberopticbronchoscopy (FOB). A thorough examination of bronchial tree was carried out and bronchoalveolarlavage (BAL) was taken and was sent for Ziehl-Neelsen staining, MGIT960 TBculture, pyogenicand fungal culture. Bronchial brushing, endo-bronchial and transbronchial lung biopsy(TBLB) wherever indicated were performed and Ziehl-Neelsen staining was performed and post bronchoscopy sputum(PBS) was also sent for Ziehl-Neelsen stain.Results are summarized in tables and percentages. Quantitative data is summarized using means& standard deviation. Cross tabulation with outcome variable of interest was done using statistical software Epi-info version 7 (7.1.1.0). A p-value of less than 0.05 was considered statistically significant.

Results: Males constituted majority of our study population. The most common age group involved in the study was 18-28 years (36.3%). cough was the most common symptom reported by 62 patients (93.93%). The past history of PTB was present 6 patients (9.09%).Majority of study population, 39 patients (59.09%) had unilateral lesion on CXR. Out of 66 clinically suspected SSN-PTB patients, 52 patients (78.7%) were finally diagnosed as having active PTB. The diagnosis other than PTB was established in 6 (9.09%) cases, which included 3 cases of fungal (Candida) pneumonia and 3 cases of bacterial (pseudomonas species, citrobacter species, serratiamarsecens) pneumonia.

Conclusions: FOB and various bronchoscopy guided procedures can provide a rapid and definitive diagnosis of PTB in sputum negative patients.

Keywords: Sputum smear negative pulmonary tuberculosis, Fiberoptic bronchoscopy, MGIT960.

INTRODUCTION

Mycobacterium tuberculosis (MTB), discovered by Robert Koch in 1882 is the leading killer of human being.[1] In 2012, WHO estimated 8.6 million incident cases of TB globally equivalent to 122 cases per 100000 population. Out of 8.6 million cases, an estimated 0.5 million were children and 2.9 million occurred among women and 1.0 to 1.2 million among people living with human immunodeficiency virus (HIV).[2] Detecting patients with active pulmonary tuberculosis (PTB) disease is an important component of tuberculosis (TB) control as early appropriate treatment renders these patients non-infectious and interrupts the chain of transmission of TB. Under the programme conditions, such as those endorsed by the World Health Organization (WHO)[3] and implemented successfully in high burden countries including India's Revised National Tuberculosis Control Programme (RNTCP)of Government of India, the diagnosis of PTB is based on sputum smear examination.[4]

However, in patients with a compatible clinical picture, sputum smears do not reveal acid-fast bacilli (AFB) in all patients. Sputum smear negative pulmonary tuberculosis (SSN-PTB) is a common clinical problem faced by the clinicians as approximately 50% of PTB cases are sputum smear negative for AFB.[5]This is particularly true in the case of children who are unable to produce an adequate sample of sputum, patients with immunosuppressed states.

Currently diagnostic criteria for SSN-PTB include at least two sputum smear negative for AFB, radiographic abnormalities consistent with active PTB, no response to a course of broad spectrum antibiotics (except in a patient for whom there is a laboratory confirmation or strong clinical evidence of HIV infection), and a decision by a clinician to treat with full course of anti TB chemotherapy.[6] A patient with

positive culture but negative AFB sputum examination is also a smear negative case of pulmonary TB. Although microscopic examination is rapid, simple and economical, it is relatively insensitive, requiring more than 10, 000 bacilli per milliliter to detect AFB. Other factors like poor quality of the sputum sample, deficiency in preparation, staining, or examination of the sputum smear can contribute to the negative results.[7] On other hand, if not treated, 64% of sputum negative suspects could need chemotherapy within 12 months.[8] Sputum culture can increase the diagnostic yield by 20-40%, although the time needed for obtaining the final result is 2-8 weeks when solid media are used or 10-40 days when automated non-radiometric systems are used.[9]ChestX-ray is also an important and widely used method for diagnosing PTB. However, it has several limitations. Chest X-ray is often unable to determine disease activity, differentiating active disease from sequelae is often difficult, and many non-tubercular diseases, such as neoplasia, pulmonary mycosis, and sarcoidosis may mimic TB radiologically.

Difficulty in diagnosis arises when a patient clinically and radiologically suspected of having active TB, but does not produce sputum. Henceforth, more aggressive procedures need to be undertaken in these patients in order to establish the diagnosis. A number of studies confirm the usefulness of fiberoptic bronchoscopy (FOB) in the diagnosis of PTB.[10-11]The main advantage of FOB is its ability to visualize the bronchial tree and collect samples directly from the site of pathology. FOB with bronchial aspiration and broncho alveolar lavage (BAL) under local anesthesia is a relatively safe procedure and well tolerated by most of the patients.[12-15] Complications are known but rare in occurrence.[16-17]

Early diagnosis of PTB prevents progression of disease, reduces morbidity and spread of disease. It also prevents permanent lung damage by fibrosis. The present study was undertaken to evaluate the role of FOB in SSN-PTB or in patients unable to produce sputum by direct visualization of bronchial tree and collecting specimens by bronchoalveolar lavage, endobronchial biopsy, transbronchial lung biopsy (TBLB) and post-bronchoscopy sputum (PBS).

METHODOLOGY

This Institutional based Prospective Study was conducted in the department of Pulmonary Medicine and Microbiology, IGMC, Shimla from July 2014 to June 2015. All consecutive patients with sputum smear negative pulmonary tuberculosis who attended the pulmonary medicine outpatient as well as inpatients were selected for the study.

Inclusion Criteria: All patients whose two sputum examination is negative for acid fast bacilli or who are unable to produce sputum and has given consent for the study.

Exclusion Criteria: Patients with Smear positive pulmonary tuberculosis, Not willing for informed consent,Pleural effusion,Pregnancy,Accessible lymph node,Contraindication to FOB,Seriously ill patients were excluded.

Procedure: Patients presenting with respiratory symptoms such as cough for at least 2 weeks duration, fever, hemoptysis, anorexia and loss of weight, and two sputum smears negative forAFB or unable to produce sputum and radiographic appearances suggestive of PTB were evaluated. Physical examination, routine investigations, and assessment of patients for the fitness of bronchoscopy procedure were done. Lignocaine sensitivity and premedication with injection atropine 0.6 mg intramuscularly were given to all patients one hour before the procedure. FOB was performed using PENTAX video bronchoscope EB-1970k with xenon light source through transnasal or oral route and all patients received lignocaine 2% topically that is necessary to minimize coughing. During bronchoscopy, patient's vital parameters such as blood pressure, heart rate, respiratory rate and oxygen saturation were monitored.All procedures were carried out as per the International recommendations.[18-19] A thorough examination of bronchial tree was carried out and bronchoalveolar lavage (BAL) was taken. Bronchial brushing, endobronchial and transbronchial lung biopsy (TBLB) wherever indicated were performed and post bronchoscopy sputum (PBS) was also sent for Ziehl-Neelsen stain. The Ziehl-Neelsen staining was performed in BAL, BB, endo-bronchial and TBLB samples also. Smears were examined under oil immersion lens. BAL sample was also sent for MGIT960 TB culture,pyogenic and fungal culture.

The data collected was entered into a computer in MS Excel spreadsheet 2007. Results are summarized in tables and percentages. Quantitative data issummarized using means& standard deviation. This was done by using MS Excel 2007. Cross tabulation with outcome variable of interest wasdone using statistical software Epi-info version 7 (7.1.1.0). A p-value of less than 0.05 was considered statistically significant. Sensitivity, specificity, positive predictive value, negative predictive value of the testswere calculated using standard statistical formulas.

RESULTS

The total Number of patients involved in the study were 66, out of which 46 (69.69%) were male and 20 (30.30%) were female. Mean age of study population was 41.18 years.Mean age among male and female were 42.35 and 38.50 years respectively.

Table 1: Result of FOB in diagnosed PTB cases

FOB Specimen	No. (%)
BAL smear for ZNS	15 (22.72)
BAL for MGIT960 TB culture	48 (72.72)
BAL for fungal culture	4 (6.06)
BAL for pyogenic culture	2 (3.03)
Bronchial brushing for ZNS	1 (1.51)
Bronchial brush for cytology	0 (0)
TBLB/Endobronchial biopsy for ZNS	0 (0)
TBLB/Endobronchial biopsy for HPE	4 (6.06)
Post bronchoscopic sputum	4 (6.06)

ZNS=Ziehl-Neelsen staining

Among 66 patients cough was the most common symptom being reported by 62 patients (93.93%), followed by dyspnea in 57 patients (86.36%), chest pain in 33 patients (50%), fever in 30 patients (45.45%), and hemoptysis in 19 patients (28.78%). Past history of PTB in 6 patients (9.09%), diabetes mellitus in 3 patients (4.54%), and hypertension in one patient (1.51%). Among patients with PTB, 19 were smoker and 33 were non-smoker, 13 patients were alcoholic and 39 were non-alcoholics. Four (6.06%) patients had family history of PTB. Chest x-ray was performed in all patients .Among patients with active PTB, 23 had right sided lesion and 8 had left sided lesion. Bilateral lesion was seen in 21 patients. 50 patients (75.76%) had infiltrates and 16 patients (24.24%) had cavitatory lesions. Based on radiological classification of disease extent by National Tuberculosis Association of USA, the lesions on CXR were classified into minimal, moderately advanced and far advanced. In our study, 31 patients (46.96%) had mild lesions, 28 patients (42.42%) had moderately advanced lesions and 7 patients (10.60%) had far advanced lesions.

Out of 66 patients, 57 were subjected to CT chest for elucidating the underlying cause and for localization, 1 patients (17.54%) were finally diagnosed as non-PTB cases and 47 patients (82.45%) were finally diagnosed as PTB. The most common radiological lesions on CT chest was consolidation seen in 30 patients (45.45%), followed by nodular opacities in 26 patients (39.39%), cavitation in 17 patients (25.75%), tree in bud appearance in 17 patients (25.75%) and consolidation with associated loss of volume in 4 patients (6.06%).The most common FOB finding was normal bronchial tree which was observed in 44 patients (66.66%). Other findings include secretions in 6 patients (9.09%), erythema and ulceration in 7 patients (10.60%), bronchial stenosis in 6 patients (9.09%), distortion in 3 patients (4.54%) and growth in one patient (1.51%).

Table 2: Sensitivity, specificity, PPV and NPV of smear in FOB specimens

FOB Specimen	BAL MGIT TB culture Positive	BAL MGIT TB culture negative	Sensitivity (%)	Specificity (%)	False –ve (%)	False +ve (%)	PPV (%)	NPV (%)
Z N Staining								
Smear Positive	11	4	22.9	77.7	77.0	22.2	73.3	27.4
Smear Negative	37	14						
Post Bronchoscopy sputum								
Smear Positive	4	0	8.3	100	91.6	0	100	29
Smear Negative	44	18						

Among the 66 patients included in the study, BAL was done in all the patients and subjected to Ziehl-Neelsen staining and MGIT960 TB culture. A positive microscopic yield was obtained in 15 (22.72%) patients, MGIT960 culture was positive in 48(72.72%) patients. Bronchial brushings was taken in 3 cases, only one bronchial brushing yielded positive result by Ziehl-Neelsen staining smear.Endobronchial biopsy was done in three cases and TBLB was done in one case. Histopathological examination revealed caseating granulomain all 4 cases. A positive post bronchoscopic sputum yield was found in 4 patients (6.06%) as shown in Table-1.

Among the 52 diagnosed cases of PTB, BAL was smear positive in 11cases, negative in 37 cases, the sensitivity and specificity being 22.9% and 77.7% respectively with PPV of 73.3% and NPV of 27.4% as shown in table-2. Similarly post-bronchoscopic sputum smear was positive in 4 cases, negative in 44 cases, the sensitivity and specificity being 8.3% and 100% respectively with PPV of 100% and NPV of 29%.

Table 3: Diagnostic yield of FOB

Diagnosis	No. (%)
Total PTB cases diagnosed	52 (78.78)
BAL with ZN staining	15 (22.72)
BAL with MGIT960 TB culture	48 (72.72)
Total cases of other diseases diagnosed	6 (9.09)
Fungal pneumonia	4 (6.06)
Bacterial pneumonia	2 (3.03)
Malignancy	0

The complications following bronchoscopic procedure were very few, minor hemorrhage following TBLB was seen only in one patient (1.51%).Serious complications like respiratory failure, cardiac arrhythmia, cardiac arrest and pneumothorax was not seen in our study group.

Among the 66 cases studied the total number of PTB cases diagnosed was 52 (78.78%) as shown in table-3. Total number of PTB cases having smear +ve on ZN staining was 15 (22.72%) and total number of PTB cases showed growth on MGIT 960 TB culture was 48 (72.72%). The total number of cases, of other diseases diagnosed was 6 (9.09%), which included 3 cases of fungal (Candida) pneumonia and 3 cases of bacterial (pseudomonas species, citrobacter species, serratiasmarsecens) pneumonia.

DISCUSSION

Despite the discovery of the tubercle bacilli more than a hundred years ago and all the advances made in our knowledge of the disease, TB is still a major health problem facing mankind, particularly in developing countries. India accounts for an estimated 2.2 million of the 8.6 million new cases of TB that occur each year globally and harbors more than twice as many cases as any other country.[2]

The mainstay of diagnosis of PTB is the detection of AFB in sputum samples. Sputum microscopy is a highly specific and low-cost test for the diagnosis of PTB. It is an essential component of the directly observed treatment short-course (DOTS) strategy of the WHO. However, sputum smear is not always positive. Smear negative, culture positive state has been observed in 22% to 61% of cases and contributes to the burden of SSN-PTB.[8,20,21.]

SSN-PTB, that includes patients with clinical and radiological evidence of pulmonary TB but repeatedly negative sputum smear for AFB, is a common clinical problem faced by the clinicians, particularly in countries affected by the dual TB/HIV epidemics. SSN-PTB is also infectious but the infectivity rate is less compared to patients with smear-positive PTB. Moreover, 50% of patients with SSN-PTB would need ATT by the end of 12 months if untreated.[8,22]Therefore, emphasis should be put on early diagnosis of SSN-PTB as early effective treatment renders the patients with active PTB non-infectious and interrupts the chain of transmission of TB.

The most remarkable advantage with the recent methods of automated mycobacterial culture lies in their earlier detection of culture-positivity. Among them the earliest and most widely studied method, viz. BACTEC-460 system, requires sophisticated instrumentation and the provision of safe handling and disposal of radioactive waste. Alternate methods like MGIT 960 and MB Redox tube systems are based on detection of fluorescent or colorimetric signals and, hence, are free from the hazards of radioactive handling.

In our study total 66 patients were included and all underwent bronchoscopy. The most common gross FOB finding was normal bronchial tree which was observed in 44 patients (66.66%). Other findings were secretions in 6 patients (9.09%), erythema and ulceration in 7 patients (10.60%), bronchial stenosis in 6 patients (9.09%), distortion in 3 patients (4.54%), and growth in one patient (1.51%). These findings are in accordance with the various other studies as by Rawat *et al.*[23]who reported normal bronchial tree in 48% patients, normal bronchial tree with secretions in 25%, normal bronchial tree with distortion in 9.6% patients, erythema, ulceration, nodularity in 36.5% patients. Growth was not seen in any patient. Kulpati *et al.*[24]observed that coating of mucosa of involved segments with yellowish white secretions in almost all patients and also revealed mild to moderate hyperemia after bronchial wash. Segmental bronchus was narrowed in 20% patients, and ulceration was seen in 20% patients. Similar observations were made by Panda *et al.*[25]According to their study, 44% had normal bronchial mucosa, 21% had unhealthy mucosa with granulations, 35% had discharge of mucous from bronchus, 5% had growth, 3% had external compression and three per cent had bleeding from bronchus and some cases had multiple findings. Quaiser *et al.*[26]revealed no lesion in 19 (47.5%) patients, gross lesion in 21 (52.5%) patients, of which 6 (15%) patients showed features suggestive of PTB (endobronchial inflammation with distortion and stenosis of bronchi`, tubercles), 8 (20%) patients had generalized chronic inflammation and 7 (17.5%) patients had features of acute inflammation.

BAL was done in all the patients and subjected to Ziehl-Neelsen staining and MGIT-960 TB culture.A positive microscopic yield was obtained in 15 patients (22.72%), MGIT960 culture was positive in 48 patients (72.72%). Bronchial brushings was taken in 3 cases, only one bronchial brushing yielded positive result by Ziehl-Neelsen staining smear. Endobronchial biopsy was done in three cases and TBLB was done in one case and histopathological examination revealed caseating granuloma in all 4 cases. A positive PBS yield was found in 4 patients (6.06%). In Rawat *et al.*[23] study culture by MGIT960 method yielded the growth of MTB in 51.9% patients, and AFB smear positive in 23% patients. Similarly Chawla *et al.*[27]showed that the positive yield of BAL smear for AFB was 20.33% and Yuksekol I *et al.*[28]showed BAL positive for AFB smear in 23% and 50% positive for culture whereasBaughman *et al.*[29]showed a positive yield by BAL fluid smear examination and MTB culture as 68% and 92% respectively which is

much higher than our study. Wongthim *et al*[30] reported BB having the highest diagnostic yield being positive in 33 of the 65 (51%; 4.6% exclusively positive) patients. In our study the low yield of bronchial brushings may be due to the fact that it was done in very few cases because majority of patients had normal bronchial anatomy. Other similar studies in the literature such as Bachh*etal.*[31]whoreported the PBS smear yield as 18.33% while Sarkar *et al.*[32] have reported a very high (73%) positive yields of PBS. In our study immediate diagnosis was possible in 28.78% cases of PTB by demonstrating positive AFB in FOB guided specimens and histopathological evidence of caseating granuloma. Sarkar et al[32]reported immediate diagnosis in 73% of cases. The yield of immediate diagnosis of active PTB in SSN-PTB suspects varies widely from 9% to 73% in the similar studies reported in the literature.[33,34,35.] The overall diagnostic yield of smear examination, MGIT 960 culture and demonstration of granuloma from various bronchoscopic specimens was found to be 78.7% (52 cases) in our study. The overall yield of FOB in the diagnosis of active PTB among SSN-PTB suspects varies widely in the literature ranging from 35.7% to 95%.[24,27,30-33,36-41.] Shin *et al.*[42]reported sensitivity, specificity, PPV and NPV of BAL for mycobacterial culture in his study as 75.9%, 97.2%, 95.3% and 84.3%respectively.Result of this study showed higher value than our study. Therefore, FOB is a useful procedure in the diagnosis of PTB.

Furthermore, Jacomelli*et al.*[43]reportedthat for the diagnosis of tuberculosis, BAL showed a sensitivity and a specificity of 60% and 100% respectively. The sensitivity and specificity in this study group was higher than our study.Therefore bronchoscopy is a safe and effective method for the diagnosis of PTB in patients in whom diagnosis by sputum smear microscopy is not possible. In the present study, FOB was useful not only for the diagnosis of tuberculosis but also for the identification of other pathologies, especially pulmonary infection. Other pathologies were diagnosed in 6 (9.09%) patients. Three patients had fungal (Candida) pneumonia and 3 patients had bacterial (Pseudomonas, citrobacter, serratiamarsecens) pneumonia. Singhal*et al.*[41] reported 64.3% cases other than active PTB including 42.9% cases of community acquired pneumonia (CAP), 7.2% cases of neoplasm, 11.9% cases of foreign bodies, and 2.3% case of ABPA.

In our study the complications following bronchoscopic procedure were very few, minor hemorrhage following TBLB was seen only in one patient (1.51%). Serious complications like respiratory failure, cardiac arrhythmia, cardiac arrest and pneumothorax did not occur in our study group. In another study assessing complications ofFOB in 1328 children, De Blic*et al.*[44]have concluded that bronchoscopy is safe in children, recording a minor complication rate of 5.2%, in the form of desaturation, excessive cough, nausea, transient laryngospasm and epistaxis and major complications occurred in 1.7% only. Sinha *et al.*[45] found as complications hypoxia (2.4%), post-bronchoscopy bleeding (1.2%), fever (1.2%), chest pain (1.7%) and pneumothorax (0.51%). The reported literature reinforces the fact that FOB in properly selectedpatients has very minimal complication rates, which was the case in our study also.

LIMITATIONS

There are few limitations in this study. Firstly, a major fraction of the recruited patients did not have significant expectoration and it was not possible to perform both sputum and BAL culture, and also owing to the fact that automated MGIT960 liquid culture is much more superior than solid culture on Lowenstein Jensen medium. Hence we decided to include only BAL samples in our study for MGIT 960 TB culture. The number of subjects was also small in our study.

CONCLUSION

India is among the 22 high burden countries of PTB, and due to high contagious nature of PTB, its early recognition is of utmost importance. The results of present study suggest that FOB is a useful tool in diagnosing SSN-PTB patients. FOB reveals a high bacteriological confirmation of diagnosis in SSN-PTB patients. FOB is also a safe procedure. FOB also helps in ruling out non-PTB conditions like bacterial pneumonia. We, therefore, conclude that FOB and various bronchoscopy guided procedures can provide a rapid and definitive diagnosis of PTB in sputum negative patients.

REFERENCES

1. Fairchild AL, Oppenheimer GM. Public health nihilism vs. pragmatism: history, politics, and the control of tuberculosis.Am J Public Health.1998 Jul; 88(7):1105-17.
2. World Health Organization- Global tuberculosis report 2013/ Global plan to stop TB. http://www.stoptb.org/news/stories/2013/ns13_067.asp (accessed 1/10/2015)
3. World Health Organization. Treatment of Tuberculosis: Guidelines for National Programmes.3rd ed. Switzerland, Geneva: WHO; 2003.(accessed on 1/10/2015)
4. TB India 2007. RNTCP Status Report. New Delhi: Central TB Division, Directorate General of Health Services, Ministry of Health and Family Welfare, Government of India; 2007.(accessed on 1/10/2015)
5. Kvale PA, Johnson MC, Wroblewski DA. Diagnosis of tuberculosis:routine cultures of bronchial washings are not indicated. Chest.1979 Aug; 76(2):140-2.
6. World Health Organization. Geneva: Treatment of Tuberculosis Guidelines. 4th edition. http://www.who.int/tb/ publications/tb_treatmentguidelines/en. (accessed on 1/10/2015)

7. Toman .K, How many bacilli are present in a sputum specimen found positive by smear microscopy? In: Frieden T, Editor- Toman's Tuberculosis Case Detection, Treatment & Monitoring: Questions & Answers, 2nd edition, Geneva: WHO; 2004; page 11-13.
8. Hong Kong Chest Service / Tuberculosis Research Center Madras/ British Medical Research Council. Sputum smear negative tuberculosis: Controlled clinical trial of 3-month and 2-month regimen of chemotherapy. Lancet. 1979; 1:1361–3.
9. Conde MB, Melo FA, Marques AM. III Brazilian Thoracic Association Guidelines on tuberculosis.J Bras Pneumol. 2009 Oct; 35(10):1018-48.
10. Fujii H, Ishihara J, Fukaura A et al. Early diagnosis of tuberculosis by fiberoptic bronchoscopy. Tubercle Lung Dis. 1993;73: 167–9.
11. Chan HS, Sun AJ, Hoheisel GB.Bronchoscopic aspiration and bronchoalveolar lavage in the diagnosis of sputum smear-negative pulmonary tuberculosis.Lung. 1990; 168(4):215-20.
12. Sharma SK, Pande JN. Fiberoptic bronchoscopy. Indian J Chest Dis Allied Sci. 1988 Jul-Sep; 30(3):163-5.
13. Reynolds HY. Bronchoalveolar lavage. Am Rev Respir Dis. 1987 Jan; 135(1):250-63.
14. Walters EH, Gardiner PV. Bronchoalveolar lavage as a research tool. Thorax. 1991 Sep;46(9):613-8.
15. Sharma SK, Pande JN. Bronchoalveolar lavage: application in pulmonary diseases. Indian J Chest Dis Allied Sci. 1990 Jul-Sep;32(3):157-76.
16. Timsit JF, Misset B, Azoulay E et al. Usefulness of airway visualization in the diagnosis of nosocomial pneumonia in ventilated patients.Chest.1996; 110:172–9.
17. Colt HG, Prakesh UB, Offord KP. Bronchoscopy in North America: survey by the American Association for Bronchology. 1999. J Bronchology 2000; 7:8-25.
18. Harrison BDW. Guidelines for care during bronchoscopy. Thorax. 1993;48:584.
19. British Thoracic Society guidelines on diagnostic flexible bronchoscopy Thorax. 2001 Feb; 56(Suppl 1): i1–i21.
20. Kim TC, Blackman RS, Heatwole KM et al. Acid-fast bacilli in sputum smears of patients with pulmonary tuberculosis. Prevalence and significance of negative smears pretreatment and positive smears post-treatment. Am Rev Respir Dis. 1984 Feb;129(2):264-8.
21. Narain R, Rao MS, Chandrasekhar P, Pyarelal. Microscopy positive and microscopy negative cases of pulmonary tuberculosis. Am Rev Respir Dis. 1971 Jun; 103(6):761-73.
22. Hong Kong Chest Service/Tuberculosis Research Centre, Madras/British Medical Research Council. A study of the characteristics and course of sputum smear-negative pulmonary tuberculosis. Tubercle.1981; 62:155–67.
23. Rawat J, Biswas D, Sindhwani G. et al. Diagnostic role of MGIT culture of bal samples in sputum smear negative pulmonary tuberculosis. Indian J Tuberc 2013; 60: 77-82.
24. Kulpati DD, Heera HS. Diagnosis of smear negative pulmonary tuberculosis by flexible fibreoptic bronchoscopy. Indian J Tuberc. 1986;33:179–82.
25. Panda BN, Rajan KE, Jena J et al. Diagnostic yield from flexible fiberoptic bronchoscopy in sputum negative pulmonary tuberculosis patients. Ind J Tuberc. 1995;42:207.
26. Quaiser S, Agarwal A, Khan R et al.Fiberoptic bronchoscopy, as a valuable diagnostic option in sputum negative pulmonary tuberculosis: A prospective study. Int J Appl Basic Med Res. 2012 Jul;2(2):123-7.
27. Chawla R, Pant K, Jaggi OP et al. Fibreoptic bronchoscopy in smear-negative pulmonary tuberculosis. EurRespir J. 1988 Oct; 1(9):804-6.
28. Yüksekol I, Bal S, Ozkan M et al. The value of fiberoptic bronchoscopy in diagnosis of smear negative pulmonary tuberculosis. TuberkToraks. 2003; 51(4):405-9.
29. Baughman RP, Dohn MN, Loudon RG et al. Bronchoscopy with bronchoalveolar lavage in tuberculosis and fungal infections. Chest.1991 Jan;99(1):92-7.
30. Wongthim S, Udompanich V, Limthongkul S et al. Fiberoptic bronchoscopy in diagnosis of patients with suspected active pulmonary tuberculosis. J Med Assoc Thai. 1989 Mar;72(3):154-9.
31. Bachh AA, Gupta R, Haq I, Varudkar HG. Diagnosing sputum/smear-negative pulmonary tuberculosis: Does fibreoptic bronchoscopy play a significant role? *Lung India* 2010;27(2):58-62.
32. Sarkar SK, Sharma GS, Gupta PR et al.Fiberoptic bronchoscopy in the diagnosis of pulmonary tuberculosis.Tubercle. 1980 Jun; 61(2):97-9.
33. So SY, Lam WK, Yu DY. Rapid diagnosis of suspected pulmonary tuberculosis by fiberoptic bronchoscopy. Tubercle. 1982; 63:195–200.
34. Russell MD, Torrington KG, Tenholder MF. A ten-year experience with fibreoptic bronchoscopy for mycobacterial isolation: Impact of the Bactec system. Am Rev Respir Dis. 1986; 133:1069–71.
35. Khoo KK, Meadway J.Fibreoptic bronchoscopy in rapid diagnosis of sputum smear negative pulmonary tuberculosis. Respir Med. 1989 Jul;83(4):335-8.
36. Mohan A, Sharma SK. Fiberoptic bronchoscopy in the diagnosis of sputum smear-negative pulmonary tuberculosis: current status. Indian J Chest Dis Allied Sci. 2008 Jan-Mar; 50(1):67-78.
37. Willcox P A, Benatar S R, Potgieter P D. Use of the flexible fibreoptic bronchoscope in diagnosis of sputum-negative pulmonary tuberculosis. Thorax. 1982 Aug; 37(8): 598–601.
38. Purohit SD, Sisodia RS, Gupta PR et al. Fiberoptic bronchoscopy in the diagnosis of sputum smear negative pulmonary tuberculosis. Lung India. 1983; 1:143–6.
39. Gracia J, Curull V, Vidal R et al. Diagnostic value of bronchoalveolar lavage in suspected pulmonary tuberculosis. Chest.1988 Feb;93(2):329-32.
40. Jaiswal AK, Kulpati DD, Jain NK, Singh MM. Role of bronchoscopy in early diagnosis of suspected smear negative cases of pulmonary tuberculosis. Indian J Tuberc. 1989;36:233.
41. Singhal S, Gaidhane A, Khatib N et al. Use of flexible bronchoscopy for rapid diagnosis of suspected tubercular cases in rural India. *J Infect Dev Ctries*2009; 3(11):860-864.
42. Shin JA, Chang YS, Kim TH, Kim HJ, Ahn CM, Byun MK. Fiberoptic bronchoscopy for the rapid diagnosis of smear-negative pulmonary tuberculosis. BMC Infect Dis2012;12:141.
43. Jacomelli M, Silva PR, Rodrigues AJ et al. Bronchoscopy for the diagnosis of pulmonary tuberculosis in patients with negative sputum smear microscopy results. J Bras Pneumol. 2012 Mar-Apr;38(2):167-73.
44. De Blic J, Marchac V, Scheinmann P. Complications of flexible bronchoscopy in children: prospective study of 1,328 procedures. EurRespir J. 2002 Nov;20(5):1271-6.
45. Sinha S, Guleria R, Pande JN et al. Bronchoscopy in adults at a tertiary care centre: Indications and complications. J Indian Med Assoc. 2004; 102:152–4, 156.