ORIGINAL RESEARCH PAPER

Pulmonary Medicine

ROLE OF BRONCHOALVEOLAR LAVAGE IN SPUTUM-SMEAR NEGATIVE, CLINICALLY AND RADIOLOGICALLY SUSPECTED NEW CASES OF PULMONARY TUBERCULOSIS

KEY WORDS: PTB, FOB, BAL, CBNAAT

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ABSTRACT

BACKGROUND – Only 50 to 60% of PTB cases are found to be sputum-smear positive. Diagnosis without bacteriological confirmation can lead to either under or over diagnosis. This study was conducted to investigate on the usefulness of BAL for the early diagnosis of new sputum-smear negative PTB cases.

OBJECTIVE – To evaluate the diagnostic yield of BAL in the microbiological confirmation of AFB in new sputum-smear negative, clinically and radiologically suspected new cases of PTB.

MATERIALS AND METHODS – 72 PTB suspected sputum-smear negative patients were subjected to FOB, and BAL samples were sent for Zeihl-Neelson staining, culture on L-J slants, and CBNAAT. The data was statistically analyzed (Graphpad Instat).

RESULTS – The diagnostic yields of BAL microscopy, BAL CBNAAT and BAL culture were found to be 43.05%, 54.17% and 55.56% respectively. Diagnostic yield when all the three investigations were combined was 58.33%. On comparing with the BAL culture results the sensitivity, specificity, PPV & NPV of BAL microscopy and BAL CBNAAT were found to be 72.5%, 93.75%, 93.55% & 73.17% and 95%, 96.88%, 97.44% & 93.94% respectively.

CONCLUSION – BAL has a significant role in the early diagnosis of sputum-smear negative PTB. CBNAAT is more sensitive and specific compared to microscopy, and rapid compared to culture method.

INTRODUCTION

Pulmonary tuberculosis is a major public concern world-wide. Even though TB incidence is falling at about 2% per year, it remains a major cause of mortality globally.

According to Global Tuberculosis Report (2018), there were an estimated 10 million new cases of TB in the year 2017[1]. In the same year, there were an estimated 558000 new cases of Rifampicin resistant TB globally[1]. India holds 24% of the aforementioned resistant population. India is the country with the highest burden of TB[2]. The incidence of TB in India in 2016 was 2.79 million cases[2]

To confirm Pulmonary TB, WHO recommends sputum-smear examination to detect acid fast bacilli (AFB) by Acid Fast staining (Zeihl-Neelson staining).About half of the active Pulmonary TB patients may fail to produce sputum, or when it is available, AFB may be negative. Previous studies show that, smear negative Tuberculosis cases appear to be responsible for 13 - 17 % of Tuberculosis transmission[3-4]. More than 50% of smear negative patients would need chemotherapy, if left untreated[5]. In such situations, physicians have to start ATT especially if there is high clinical and radiological suspicion. But the disadvantage is that, most of the clinical and radiological features associated with Pulmonary TB have low specificity, which may lead to false diagnosis, ultimately resulting in people being wrongly enrolled on Anti-TB treatment. These people get unnecessarily exposed to the toxicity of prolonged treatment, and economic burden.

Since the diagnosis based only on clinical and radiological suspicion can lead to either under or over diagnosis, making use of samples other than sputum for the microbiological confirmation is relevant. Fiber Optic Bronchoscopy (FOB) is an alternative method for collecting respiratory samples, which can help in such situations. The present study assessed the usefulness of Broncho Alveolar Lavage (BAL) for the early diagnosis of sputum-smear negative new Pulmonary TB cases.

MATERIALS AND METHODS

This is a prospective analytical study conducted in the Department of Pulmonary Medicine, R.N.T Medical College, Udaipur, Rajasthan from October 2016 to September 2017.

Patients admitted with clinical and radiological suspicion of Pulmonary TB without previous history of taking ATT from any source were considered for study. In these patients, one spot and one over-night sputum samples were collected and sent for AFB examination and reports were collected. Patients with either one or both sputum-smears positive for AFB were excluded from the study. Patients with both sputum-smears negative for AFB were enrolled, and written informed consents for FOB were obtained.

After giving proper pre-medications, FOB was done under conscious sedation, and BAL was collected from the affected area.

The collected BAL samples were sent under aseptic precautions for 3 separate investigations.

1) *Zeihl-Neelson staining* – Smear was examined under oil-immersion lens for the presence of AFB. About 100 fields were examined for bacilli before reporting as negative.
2) *Culture on L-J slants* – Samples were incubated at 37°C and screened for any growth at regular intervals of two times a week. Culture were considered negative for AFB if no growth was observed after incubation of Lowenstein – Jensen (L-J) slants for a period of 10 weeks.
3) *Gene Xpert or CBNAAT* (Cartridge Based Nucleic Acid Amplification Test). This test can give report within 2 hours. It can give report on Rifampicin Resistance too, which ultimately helps for the early detection of MDR-TB cases.

Data Analysis:

All the collected data were entered in software Graphpad Instat, and results were analyzed using appropriate statistical tests. P-value less than 0.05 was taken as statistical significant difference.

Exclusion Criteria:

1) Sputum-smear positive cases
2) Patients who have previous history of taking ATT from any source
3) People who are physically unfit for undergoing FOB

4) HIV seropositive patients
5) Patients not willing for informed consent

RESULTS

In the present study, there were 66.67% male and 33.33% female patients, and male to female ratio was 2:1. Most common age group in this present study was 41-60 years. Mean age of the study population was 44.80 years. Most of the patients in the study group were either current smokers or ex-smokers. But no statistical association was found between smoking and positive BAL result. BMI of 54.17% patients were below 18.5 kg/m² (underweight). About 2/3rd of the underweight patients were ultimately found to be BAL positive for MTB.

Cough and anorexia were the most common respiratory and constitutional symptoms respectively. Anorexia, fever and night sweat were more specifically seen in patients who ultimately turned to be BAL positive. Right middle zone was the most commonly involved zone (52.78% patients). 51.39% patients presented with moderately advanced lesion on the x-ray, while 37.5% patients had minimal disease and 11.11% had far advanced disease at presentation There was no statistically significant relation between radiological extent of disease and positive BAL result. Among the 45 patients who had consolidation on chest x-ray, 33 (73.33%) were ultimately found to be MTB positive, whereas among the 27 patients who had either nodular/military lesions, only 9 (33.33%) were positive. MTB was detected in BAL samples of 6 (85.71%) out of 7 patients presented with cavity on x-ray (Table-1)

BAL Culture gave the highest diagnostic yield (55.56%). It gave positive result in 40 out of 72 patients. CBNAAT gave positive result in 39 patients (diagnostic yield - 54.17%). AFB smear gave the least diagnostic yield – 31 positive results (43.05%). Overall diagnosis could be established in 42 patients. I.e. diagnostic yield when all the three investigations combined was **58.33%** (Fig-1)

Out of the 40 cases where culture gave positive result, AFB smear and CBNAAT could diagnose only 29 and 38 cases respectively. At the same time, out of the 32 cases where culture gave negative result, AFB smear and CBNAAT could rule out presence of bacilli in 30 and 31 cases respectively (Tables-2 & 3). Out of the 39 cases where CBNAAT gave positive result, AFB smear could diagnose only 30 cases. At the same time, out of the 33 cases where CBNAAT gave negative result, AFB smear also ruled out presence of bacilli in 32 cases (Table-4)

On comparing with the culture of BAL on LJ medium, which is considered as the gold standard investigation, the sensitivity, specificity, PPV and NPV of BAL AFB smear are 72.5%, 93.75%, 93.55% and 73.17% respectively. The sensitivity, specificity, PPV and NPV of BAL CBNAAT compared to LJ-culture are 95%, 96.88%, 97.44% and 93.94% respectively.

Among the 72 patients, 4 of them were found to have BAL samples resistant to Rifampicin; where as remaining 68 had BAL samples sensitive to Rifampicin, by CBNAAT.

Table-1: Distribution of BAL positive and BAL negative patients based on sex, age, smoking status, BMI, symptoms and radiological findings; and assessment of statistical significance

	BAL positive for MTB (42/72)	**BAL negative for MTB (30/72)**	**Statistical significance**
Sex			
Male	28/72(38.89%)	20/72(27.78%)	
Female	14/72(19.44%)	10/72(13.89%)	
Age, yrs			
< 20	4/72(5.56%)	1/72(1.39%)	
21-40	17/72(23.61%)	10/72(13.89%)	
41-60	17/72(23.61%)	12/72(16.67%)	
61-80	4/72(5.56%)	6/72(8.33%)	
>80	0	1/72(1.39%)	
Smoking status			
Current smokers	23/42(54.76%)	16/30(53.33%)	p=0.28 (no statistical association was found between smoking and positive BAL result)
Ex-smokers	6/42(14.29%)	1/30(3.33%)	
Non-smokers	13/42(30.95%)	13/30(43.33%)	
BMI			
< 18.5(underweight)	28/42(66.67%)	11/30(36.67%)	p=0.01(Statistically significant reduction in BMI was found in patients with positive BAL result)
18.5-24.9(normal wt)	14 /42(33.33%)	19/30(63.33%)	
25-29(overweight)	0	0	
>30(obese)	0	0	
Symptoms			
Cough	36/42(85.71%)	27/30(90%)	p=0.59(Not Significant)
Dyspnoea	24/42(57.14%)	14/30(46.67%)	p=0.38(Not Significant)
Chest pain	16/42(38.10%)	13/30(43.33%)	p=0.65(Not Significant)
Blood in sputum	10/42(23.81%)	7/30(23.33%)	p=0.96(Not Significant)
Constituitional symptoms			
Fever	33/42(78.57%)	13/30(43.33%)	p=0.002(Significant)
Night sweat	21/42(50%)	5/30(16.67%)	p=0.004(Significant)
Anorexia	35/42(83.33%)	16/30(53.33%)	p=0.006(Significant)
Loss of weight	15/42(35.71%)	6/30(20%)	p=0.15(Not Significant)
Unilateral/Bilateral lesions			
Unilateral	23/42(54.76%)	18/30(60%)	p=0.66(Positive BAL result has no statistically significant relationship on whether the patient is having unilateral or bilateral lesions on Chest x-ray)
Bilateral	19/42(45.24%)	12/30(40%)	
Radiological extent of disease			
Minimal	14/42(33.33%)	13/30(43.33%)	p=0.39(Not Significant)
Moderately advanced	24/42(57.14%)	13/30(43.33%)	p=0.25(Not Significant)
Far advanced	4/42(9.42%)	4/30(13.33%)	p=0.61(Not Significant

Type of lesion			
Consolidation	33/45(73.33%)	12/45(26.67%)	p<0.001(Highly Significant)
Nodular / Miliary	9/27(33.33%)	18/27(66.67%)	p<0.001(Highly Significant)
Cavity	6/7(85.71%)	1/7(14.29%)	p<0.001(Highly Significant)

Table-2: Distribution of study population according to BAL AFB smear and BAL culture results (N = 72)

	BAL culture positive	BAL culture negative	Total
BAL AFB smear positive	29	2	**31**
BAL AFB smear negative	11	30	**41**
Total	**40**	**32**	72

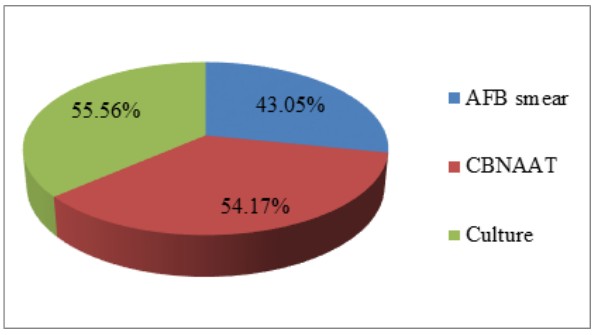
TABLE-3: Distribution of study population according to BAL CBNAAT and BAL culture results (N = 72)

	BAL culture positive	BAL culture negative	Total
BAL CBNAAT positive	38	1	**39**
BAL CBNAAT negative	2	31	**33**
Total	**40**	**32**	72

Table-4: Distribution of study population according to BAL AFB smear and BAL CBNAAT results (N = 72)

	BAL CBNAAT positive	BAL CBNAAT negative	Total
BAL AFB smear positive	30	1	**31**
BAL AFB smear negative	9	32	**41**
Total	**39**	**33**	72

Fig-1: Diagnostic yields of various investigations



DISCUSSION

In our study, highest diagnostic yield was given by of BAL Culture (55.56%). Most of the previous articles (Dimple Kumar Bhaglani *et al*[6]- 72.72%, Sandeep Gupta *et al*[7] - 78.3% and Usha Kalawat *et al*[8] - 82.3%) show a highly positive results for BAL culture, while some studies (Charoenratanakul *et al*[9]- 15%, Sharma Shubhkaran *et al*[10] - 6.4% and Liam C K *et al*[11] - 7.4%) show very low values. Our results were comparable with the results given by studies of Ritesh Kamal *et al*[12] (60%) and Prasanth Prakash *et al*[13](42%).

The diagnostic yield of BAL CBNAAT was 54.17% in our study. It shows huge differences on various studies. In the studies conducted by Jung Ar Shin *et al*[14], Brugiare.O *et al*[15], Kanwal Fatima *et al*[16] and Liam C K *et al*[11] positive BAL CBNAAT results were found in 26.19%, 33.33%, 87.09% and 80.9% cases respectively. Our result is comparable with the results found in the studies of Sanjay Avashia *et al*[17] (47.22 %).

In our study, BAL AFB smear gave diagnostic yield of 43.05%. This also shows huge variation in various articles. In the studies conducted by Usha Kalawat *et al*[8] and Raj Kumar *et al*[18], BAL AFB smears were positive in 64.70% and 51.5% cases respectively, while many other articles show very low value for BAL AFB smear. The diagnostic values of BAL AFB smear in the studies conducted by Charoenratanakul *et al*[9], Dimple Kumar Bhaglani *et al*[6], Vishal Chopra *et al*[19], Jung Ar Shin *et al*[14], Liam C K *et al*[11], Adesh Kumar *et al*[20] and Sharma Shubhkaran *et al*[10] were 7.5%, 22.72%, 19.30%, 11.11%, 8.8%, 18.5% and 3.6% respectively. Our result is comparable with the results of studies conducted by J.Balakrishna *et al*[21] (40%), Prasanth Prakash *et al*[13] (38%) and Novin Nikhbaksh *et al*[22] (38%).

On comparing with the culture of BAL on LJ medium, the sensitivity, specificity, PPV and NPV of BAL AFB smear in our study were 72.5%, 93.75%, 93.55% and 73.17% respectively. In the study conducted by Novin Nikhbaksh *et al*[22], **sensitivity, specificity, PPV and NPV were found to be 60%, 91%, 89% and 64%, respectively.** Even though the sensitivity of BAL AFB shows huge variation in various studies, it is highly specific (77% to 100%) in the studies conducted by Dimple Kumar Bhaglani *et al*[6] and Monika Agrawal *et al*[23]

In our study, the sensitivity, specificity, PPV and NPV of BAL GeneX-pert compared to LJ-culture are 95%, 96.88%, 97.44% and 93.94% respectively. The sensitivity, specificity, PPV & NPV of BAL GeneX-pert in the studies conducted by Coenraad Koegelenberg *et al*[24] and Dewald A Barnard *et al*[25] were 88.1%, 98.6%, 82.2% & 92.5% and 92.3%, 87.7%, 80% & 95.5% respectively. Similar results were found in the studies conducted by Seung Hyun Lee et *al*[26] and Monika Agrawal *et al*[23]. Almost all previous articles show high sensitivity and specificity values for BAL GeneXpert, when compared to the sensitivity and specificity values of BAL AFB.

In our study, all the three investigations gave positive results in 29 out of 72 cases, while all of them gave negative results in 30 cases.

In 9 cases, only AFB smear gave negative result, but CBNAAT and culture gave positive results. At the same time, there was no such case where only CBNAAT gave negative result. This shows that AFB smear is less sensitive compared to CBNAAT. 10000 bacilli/ml is needed for detection of bacilli by AFB smear. At the same time, only 150 bacilli/ml is needed for detection of bacilli by CBNAAT.

There was only 1 case where, only culture gave negative result, but detected by both microscopy and CBNAAT. This is possible when the BAL sample contained dead bacilli only, which could be detected by both microscopy and CBNAAT, while couldn't be grown in culture (AFB smear and CBNAAT can't differentiate between viable and dead bacilli. ZN technique can stain dead bacilli too. CBNAAT can detect DNA from a dead bacilli too[27-31]). Other possibilities for the negative result in culture could be (1) delayed culture inoculation, (2) patient might have already taken an insufficient dose/duration of ATT which could suppress the growth (wrong ATT history), and (3) BAL sample could be contaminated with other bacteria (4) technical error (5) untrained staff

In 1 case, only AFB smear gave positive result, CBNAAT and culture were negative. Non Tuberculous Mycobacteria (NTM) is a possibility in this case, as CBNAAT also failed to detect bacilli. Both MTB and NTM are acid fast (AFB microscopy can't differentiate between these two), but CBNAAT can differentiate between Myocobacterium Tuberculosis and NTM.

In 2 cases, only culture could give positive result, both AFB smear and CBNAAT gave negative results. In this case, the bacterial load might be too low for the CBNAAT to detect the DNA of bacilli. There was no such case where only CBNAAT gave positive result.

Among the 72 patients, 4(5.56%) of them were found to have BAL samples resistant to Rifampicin (primary drug

resistance). 4.17% and 4.8% cases were found to be resistant to Rifampicin in the studies conducted by Sanjay Avashia *et al*[17] and Patil Shital *et al*[32] respectively. Our results on the prevalence of Rifampicin resistance are consistent with the above studies.

Limitations of the study:

This study was limited exclusively to the patients attending the Pulmonary Medicine Department, Bari (patients coming mainly from Rajasthan, MP and Gujarat). So the results of our study are not representative of whole community. As we did not carry out Drug Susceptibility Testing (DST) of Anti Tuberculosis Drugs, we could not compare the Rifampicin resistance report by Gene Xpert with the gold standard L-J DST.

CONCLUSION

FOB is a safe procedure with minimal complications in hands of an expert. FOB guided BAL samples are very useful for the rapid and definitive diagnosis of sputum-smear negative patients with strong clinical and radiological suspicion of Pulmonary Tuberculosis. Even though, culture is considered as the gold standard investigation, it takes long time (about 8 weeks) to give the result, whereas Gene Xpert can give result in less than 2 hours. It has a higher sensitivity than AFB smear microscopy in respiratory samples. It simultaneously detects Rifampicin resistance too. This study suggests that, in tertiary care hospitals, it is justifiable to consider BAL samples in sputum-smear negative PTB suspected patients. This allows appropriate treatment to be started early with confidence, thus risks of untreated TB to both patients as well as community can be minimized.

REFERENCES

1. Global Tuberculosis report 2018.
2. TB Statistics,India–TBFACTS.ORG.Available from:https://www.tbfacts.org
3. Behr MA,Warren SA,Salmon H,Hopewell PC,Ponce de Leon A,Daley CL,Small PM. Transmission of Mycobacterium Tuberculosis from patients smear negative for acid-fast bacilli.Lancet 1999;353:444-9.
4. Alma Tostmann,Sandra V Kik,Nico A Kalisvaart,Maruschka M Sabek,Suzanne Verver,Martin J Boeree,Dick van Soolingen.Tuberculosis in a large cohort in the Netherlands.Clinical Infectious Diseases.2008;47:1135–42.
5. Hong Kong Chest Service/Tuberculosis Research Centre,Madras/British Medical Research Council.A controlled Trial of 2-month,3-month, and 12-month regimens of Chemotherapy for Sputum smear-negative Pulmonary Tuberculosis: The results at 30 months.Am Rev Respir Dis.1981;124(2):138-42.
6. Dimple Kumar Bhaglani,Malay Sarkar,Digvijay singh,Rameshwar S Negi,Sunil Sharma. Role of FOB in sputum smear negative pulmonary TB.National Journal of Medical Research.2016;6(2):134-8.
7. Sandeep Gupta,Kanu Goel.Role of Bronchoalveolar Lavage in the Diagnosis of Sputum Smear Negative Tuberculosis.J Pulmon Resp Med.2012;S6:002.
8. Usha Kalawat,Krishna K Sharma,Prakash N R Reddy,A.Gururaj Kumar.Study on BAL in clinically and radiologically suspected cases of pulmonary Tuberculosis.Lung India.2010;27(3):122-4
9. S.Charoenratanakul,W.Dejsomritrutai,A.Chaiprasert.Diagnostic role of FOB in suspected smear negative pulmonary tuberculosis.Respir Med.1995 Oct;89(9):621-3.
10. Sharma shubhkaran,Luhadia S K,Gupta N K.Diagnostic yield of FOB in sputum smear negative and radiologically suspected old cases of pulmonary tuberculosis. International Journal of Medical Science and Education.2014;1(2):68-74.
11. Liam C K,Chen Y C,Yap S F,Srinivas P,Poi P J.Detection of MTB in BAL from patients with sputum smear negative pulmonary tuberculosis using PCR assay.Respirology 1998 Jun;3(2):125-9.
12. Ritesh Kamal,Rakesh Sharma,Tushar Sahasrabuddhe,Samantha K Dash,Mujeeb Showkat,Nitin S Gaikwad.A prospective study to evaluate the utility of bronchoalveolar lavage by fiberoptic bronchoscopy in sputum smear negative patients with high suspicion of pulmonary tuberculosis. Medical Journal of Dr DY Patil Vidyapeeth.2012;5(1):43-46
13. Prashant prakash,Pooja Agarwal,Prabhat Agarwal,Durga Prasad Singh,Ashutosh Gupta.Role of bronchoscopy in diagnosing sputum smear-negative pulmonary tuberculosis.Annals of Applied Bio-Sciences.2016;3(1):113-17.
14. Jung Ar Shin,YoonSoo Chang,TaeHoon Kim,HyungJung Kim,ChulMin Ahin,MinKwang Byun.FOB for the rapid diagnosis of smear negative pulmonary TB.BMC Infectious Diseases 2012;12:141.
15. Brugiere O,Vokurka M,Lecossier D,Mangiapan G,Amrane A,Milleron B.Diagnosis of smear negative pulmonary tuberculosis using sequence capture polymerase chain reaction.Am J Respir Crit Care Med.1997;155(4):1478-91.
16. Kanwal Fatima Khalil,Tariq Butt.Diagnostic Yield of Bronchoalveolar Lavage Gene Xpert in Smear Negative and Sputum-Scarce Pulmonary Tuberculosis.Journal of the College of Physicians and Surgeons Pakistan.2015;25(2):115-8
17. Sanjay Avashia,Satyadeo Choubey,Satyendra Mishra,Atul Kharate.To Study The Usefulness Of CBNAAT(Cartridge Based Nuclear Acid Amplification Test) In BAL (Bronchoalveolar Lavage) Samples In The Diagnosis Of Smear-Negative/Non Sputum Producing Patients With Suspected Tuberculosis.J Evolution Med Dent Sci.2016 Jan;5(1):55-59.
18. Raj Kumar,Mandeep Singh,Nitesh Gupta,Nitin Goel.Bronchoscopy in immediate diagnosis of smear negative tuberculosis.Pneumonol. Alergol.Pol.2014;82:410-4.
19. Vishal Chopra,Akhil D Goel,Hardik Jain,Ashrafjit S Chahal,Arjun Bhatagar,Vidhu Mittal.Bronchoscopy in sputum smear negative patients:How relevant is it?.Int J Med Res Prof.2017;3(2):209-11.
20. Adesh Kumar,Ashish Gupta,Mohd.Haroon Khan.Role of FOB in suspected sputum-smear negative pulmonary TB cases at microscopy centre under RNTCP.Int J Med Sci Public Health.2014;3(1):31-34.
21. J.Balakrishna,P.R.Shahapur,P.Chakradhar,S.Sreedevi,Shaik Hussain Saheb.Role of FOB in sputum-smear negative,radiological suspect cases of Pulmonary TB.J.Pharm.Sci& Res.2015;7(4):231-233.
22. Novin Nikbakhsh,Masomeh Bayani,Sepideh Siadati.The value of BAL in the diagnosis of sputum smear negative pulmonary tuberculosis.Iranian Journal of Pathology.2015;10(1):35-40.
23. Monika Agrawal,Ashish Bajaj,Vinay Bhatia,Sarjana Dutt.Comparative Study of Gene Xpert with ZN Stain and Culture in Samples of Suspected Pulmonary Tuberculosis.J Clin Diagn Res.2016 May;10(5):DC09–DC12
24. Coenraad Koegelenberg,Dewald Bernard,Johannes Bruwer,Dante Plekker,Andrew Whitelaw,Jacobus Deetlefs, et al.The utility of Xpert MTB/RIF performed on bronchial lavages obtained from patients with suspected pulmonary tuberculosis.European Respiratory Journal2015;46:PA1530.
25. Dewald A Barnard,Elvis M Irusen,Johannes W Bruwer,Dante Plekker,Andrew C Whitelaw,Jacobus D Deetlefs et al.The utility of Xpert MTB/RIF performed on bronchial washings obtained in patients with suspected pulmonary tuberculosis in a high prevalence setting.BMC Pulmonary Medicine.2015;15:103.
26. Seung Hyun Lee,Jeongmin Hong,Byunghan Ryu,Min Jae Kim,Yong Pil Chong,Sang-Oh Lee et al.Diagnostic Usefulness of Bronchoalveolar Lavage Fluid Xpert MTB/RIF in Patients with Suspected Pauci-bacillary Pulmonary Tuberculosis.Open Forum Infect Dis.2017Fall 4(Suppl 1):S621.
27. Mohanjeet Kaur,Ashish Chawla.Available Diagnostic Tools in Mycobacteriology:A Recap on Utility.Medicine Update 2017,Volume 2,Chapter 21.p.91-97.Available from:www.apiindia.org
28. Supriya Sarkar.Molecular Diagnosis of Tuberculosis. Medicine Update 2017,Volume 2,Chapter 22.P.98-101.Available from:www.apiindia.org
29. Mark P Nicol. Xpert MTB/RIF:monitoring response to tuberculosis treatment.Lancet Respiratory Medicine.2013 Aug;1(6):427-8.
30. Catharina C. Boehme,M.D,Pamela Nabeta M.D,Doris Hillemann, Ph.D.,Mark P. Nicol, Ph.D,Shubhada Shenai, Ph.D.,Jenny Allen et al.Rapid Molecular Detection of Tuberculosis and Rifampin Resistance.N Engl J Med.2010;363(11):1005-15
31. Patil Shital,Halkanche Gajanan,Ayachit Rujuta. Role of Nucleic acid Amplification Tests(NAATs) in Tuberculous Pleural Effusion:Where it fits in routine diagnostic workup?.J Cell Sci Ther.2014 Jan;5(4)
32. Patil Shital,Agarwal Kailash,C.R. Chaudhary. Gene Xpert MTB/RIF assay in bronchoscopy guided bronchial wash specimens in sputum negative pulmonary tuberculosis:Sensitive,rapid and most useful test for drug sensitive and drug resistant tuberculosis.European Respiratory Journal.2016;48:PA2773.