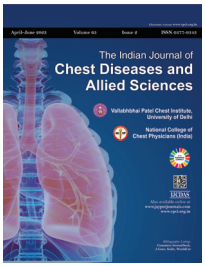
ORIGINAL ARTICLE

Microbial, Cytological, and Histopathological Analysis of Bronchoalveolar Lavage and Transbronchial Lung Biopsy in Diagnosis of Community-acquired Pneumonia: A Prospective Study



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Abstract

Background: In India, the incidence of community-acquired pneumonia (CAP) is 4 million cases per year, with 20% requiring hospitalization. A causative agent may not be isolated in about half of the cases despite careful testing. There is a paucity of data regarding the role of bronchoscopy with bronchoalveolar lavage (BAL) coupled with transbronchial lung biopsy (TBLB) in the diagnosis of CAP in the Indian population. This research aimed to evaluate the microbial, cytological, and histopathological analysis of BAL and TBLB in the diagnosis of CAP.

Materials and methods: This prospective observational study was conducted on 54 patients aged above or equal to 18 years of either sex who presented as CAP and were either immunocompromised, had non-responding pneumonia, or had radiology suggestive of atypical involvement of the lung. The BAL and TBLB with relevant microbiological, cytological, and histopathological investigations were carried out. The primary objective was to find the diagnostic yield of BAL and TBLB in patients presenting with CAP. The statistical agreement between the two diagnostic methods was tested using the Cohen–kappa technique. The sensitivity and specificity were calculated using the appropriate gold standard.

Results: The diagnostic yield was 75.9% on BAL, 94.4% on TBLB, and 100% with combined use of both BAL and TBLB. The sensitivity of BAL and TBLB was 91.1 and 88.9%, respectively, in the diagnosis of CAP. Forty-three (79.6%) patients showed infective pathogens, such as *Pseudomonas aeruginosa* (18.5%), *Klebsiella pneumoniae* (16.6%), *Mycobacterium tuberculosis* (18.5%); 9 patients (16.6%) were having non-infective etiology; while 2 patients (3.7%) were having combined etiology (infective + non-infective). Rare causes such as *Mucormycosis* 2 (3.7%), *Nocardia* 3 (5.6%), *Pneumocystis jiroveci* pneumonia (PJP) 2 (3.7%), and *Aspergillosis* 4 (7.4) which presented as necrotizing pneumonia were also identified.

Conclusion: Bronchoalveolar lavage and TBLB have a good diagnostic yield in patients presenting as CAP.

Keywords: Bronchoalveolar lavage, Community-acquired pneumonia, Diagnostic yield, sensitivity, Specificity.

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Abbreviations used in this Article

AFB = Acid-fast bacilli; BAL = Bronchoalveolar lavage; BAP = Blood agar plate; BOOP = Bronchiolitis obliterans organizing pneumonia; CAP = Community-acquired pneumonia; CFU = Colony-forming unit; CHOCA = Chocolate agar; COPD = Chronic obstructive pulmonary disease; CT = Computed tomography; ECG = Electrocardiogram; HSP = Hypersensitivity pneumonitis; ICU = Intensive care unit; NPV = Negative predictive value; NSC = Non-small cell; PCR = Polymerase chain reaction; PJP = *Pneumocystis jiroveci* pneumonia; PPV = Positive predictive value; SD = Standard deviation; SPSS = Statistical Package for Social Sciences; TBLB = Transbronchial lung biopsy; WBC = White blood cells; ZN = Ziehl–Neelsen.

Introduction

An inflammation and consolidation of lung tissue is called pneumonia. Bacteria, viruses, or fungi can cause pneumonia. It is often underestimated, misdiagnosed, and mistreated in spite of being the cause of significant mortality and morbidity. A diagnosis of pneumonia is often made on clinical grounds—history, clinical examination, and radiography such as X-ray, computed tomography (CT) scan, etc., Gram stain and culture of sputum, blood culture, bronchoscopic evaluation, polymerase chain reaction (PCR), and other various investigations.[1,2] A review of the experience of medicare for hospitalized community-acquired pneumonia (CAP)

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in 2009 reported a microbial diagnosis was made in less than 10% of cases. An increase in deaths of CAP may be due to delays in the diagnosis and treatment. Some of the causes of non-resolving pneumonia are improper diagnosis, insufficient antibiotic therapy, decreased host defense, atypical organisms, resistant organisms, etc.[3–7]

Documentation of unanticipated organisms narrows early empirical treatment, curtails antibiotic selection procedure, and reduces the danger of resistance. Patients showing slow response to therapy or if their condition is worsening, are recommended for reevaluation possibly with a CT scan or bronchoscopic procedure. It is reported that bronchoscopy with bronchoalveolar lavage (BAL) and transbronchial lung biopsy (TBLB) can effectively diagnose about 90% of patients who ultimately have a precise diagnosis.[8]

In India, the annual occurrence of CAP is 40 lakhs cases of which 20% need hospitalization. The death rate of CAP patients is 1–5%, and 25% in outpatient settings and intensive care units (ICUs) respectively. Twenty-three percent of the world's CAP patients are reported in India with case fatality rates between 14 and 30%. *Streptococcus pneumoniae* is the main cause of pneumonia.[9] Even if careful testing is done a causative organism may not be isolated in about 50% of patients. There is a paucity of data regarding BAL and TBLB in the diagnosis of CAP in the Indian population. The current study was conducted to evaluate the microbial, cytological, and histopathological analysis of BAL and TBLB in the diagnosis of CAP.

Materials and Methods

This prospective observational research was conducted from June 2021 to June 2022 in the wards and ICUs of a tertiary care hospital in Pune, Maharashtra, India. The study was approved by the institutional ethics committee (Letter #RECH/ECBHR/2020-21/164). All the patients gave written informed consent. Fifty-four patients aged above or equal to 18 years who were immunocompromised having pneumonia, non-responding pneumonia, and radiology suggestive of atypical involvement of lung were included. Patients having contraindications to the procedure (BAL and TBLB) and having prior etiological diagnosis of pneumonia were excluded.

After selection, a complete history was obtained either from the patients or relatives. A socioeconomical background of the family, initial symptoms, and clinical examination were noted in a pretested study proforma. Furthermore, BAL and TBLB with relevant microbiological, cytological, and histopathological investigations were carried out. The patients were followed till their stay or death in the hospital.

Technique of Bronchoalveolar Lavage

Flexible bronchoscopy was performed under local transtracheal anesthesia with monitoring of blood pressure, heart rate, electrocardiogram (ECG), respiratory rate, pulse, and oxygen saturation via oximeter. Also, BAL was performed from desired segments before the biopsy. Once the lavage site was chosen, the bronchoscope (PENTAX company, from Tokyo, Japan) was advanced into a subsegmental bronchus until the lumen was occluded. A sterile saline was injected. Moreover, BAL typically involved the delivery of a total of 100–240 mL of fluid in 20–60 mL aliquots; 2–3 sequential aliquots of 40–60 mL each were used. After the first aliquot of saline was infused, it was recovered immediately into the mucus extractor by gentle suction.

Technique of Transbronchial Lung Biopsy

After the introduction of a bronchoscope, the distal end of the bronchoscope was positioned close to the lesion or in the airway leading to the lesion or area of interest, as determined from imaging studies. Afterward, the biopsy forceps were advanced through the working channel of the bronchoscope until the tip was seen emerging from the distal end of the bronchoscope. The forceps and the biopsy specimen were pulled out through the working channel of the bronchoscope, and the tissue sample was inspected. After inspection, the sample was removed from the forceps tip and was collected in saline (e.g., for microbiologic analysis) or a fixative (e.g., formalin for histological analysis). The segment was blocked to achieve hemostasis by wedging.

Filtration of the fluid through sterile cotton gauze or nylon mesh was performed for cell counting to prevent the mixing of mucus with the cell pellet after centrifugation. Samples of all the patients were examined by Gram stain, Ziehl–Neelsen (ZN) stain, GeneXpert, culture on blood agar, and wherever necessary other stains and cultures were performed. The presence or absence of white blood cells (WBC) and mucus was evaluated by scanning under low power. When no WBCs were seen on the Gram stain but abundant epithelial cells were present, the smear was examined for organisms but the clinical correlation was a must. The slide was examined under oil immersion (100× objective). If the specimen contained WBCs, the examination was concentrated on areas where WBCs were seen—if one organism predominated in areas of inflammation, that is, where many WBCs were present, the organism was reported. Smears that showed no organisms were reported as "No organisms seen." The result of the Gram stain was used to guide the examination of culture plates. Reporting of the result of Gram stain and evaluation was done by Murray Washington Grading system.[4]

Furthermore, Zn stain was also performed to find acid-fast bacilli if any, and reported accordingly. As per clinical indication, Gomori Methenamine Silver stain for *Pneumocystis jiroveci* pneumonia (PJP) and fungus was performed. GeneXpert was performed by real-time PCR method using GeneXpert Ultra kit manufactured by the bioMérieux biotechnology company based in France. Culture media such as blood agar plate (BAP), chocolate agar (CHOCA), Sabouraud dextrose agar, potato dextrose agar, [aerobic/anaerobic culture, acid-fast bacilli (AFB) culture, fungal culture] were used. Specimens were plated onto BAP and CHOC. All plates were incubated in 5–7% CO_2 at 35°C. All plates were examined after 24 hours of incubation. The remaining plates were reincubated and examined after an additional 24 hours. When there was no growth, plates were discarded.

Quantification of Bronchoalveolar Lavage Specimen

- A 0.1-mL specimen was inoculated on BAP, CHOC with a 0.1-mL calibrated loop.
- The plate was then streaked so as to achieve the spread of colonies in order to enable colony count.
- Plates were incubated in 5–7% CO_2 at 35°C.
- Plates were examined after 24 hours of incubation.

Quantitation of Growth

Using the following formula, quantification was performed:

- Colony-forming unit (CFU)/mL = Number of colonies per plate × 100 (dilution factor).
- Interpretation—a colony count of 10^4 CFU/mL in BAL fluids was considered clinically significant.
- Sensitivity testing was done by the automated VITEK® method.

The TBLB specimen was sent to a laboratory where processing was done using formalin, acetone, and xylene followed by mold making, cutting the mold, preparation of slide, and examination under a microscope followed by reporting. The primary objectives were the diagnostic yield of BAL and TBLB in CAP, that is, identification of etiologic agents if any causing pneumonia, leading to appropriate diagnosis.

On the basis of a previously published study,[10] a sample size of 53 patients was calculated by the following formula:[11] $N = (Z\alpha)^2 Sn (1 - Sn)/L^2$ (prevalence), where $Z\alpha$ is a standard normal variate at 5% type 1 error ($p < 0.05$) = 1.96, Sn = anticipated sensitivity, and L is absolute precision desired on either side (half-width of the confidence interval) of sensitivity.

Statistical Analysis

Data collected was entered in Excel 2019, and analysis of data was done using statistical package for social sciences (SPSS) for Windows, Version 24, IBM Corporation, USA. The continuous data are presented as the mean and standard deviation (SD), whereas the discrete data are presented as numbers and percentages. Comparisons between two discrete variables were performed using the Chi-square test or Fisher's exact test. The statistical agreement between two diagnostic methods was tested using Cohen–kappa technique. The diagnostic efficacy indices such as sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and accuracy was calculated using appropriated gold standard. A p-value less than 0.05 was considered to be statistically significant.

Results

Table 1 shows the baseline characteristics of the study participants. The average age ± SD of the study participants was 56.9 ± 13.5 years with range of 25–84 years. Out of 54 patients, 44 were given empirical antibiotics. Of these 44 patients, antibiotic regime was changed in 33 (75%) patients after the procedure of BAL and TBLB according to the detection of the microorganisms. The duration of hospital stays and the incidence of mortality of the study participants is depicted in Table 2.

The final diagnosis was obtained in 41/54 (75.9%) patients on BAL, whereas 51/54 (94.4%) cases were diagnosed on TBLB. A combined BAL and TBLB provided a diagnosis in all the 54 cases (100%). Thirteen undiagnosed cases on BAL were diagnosed by TBLB, whereas three undiagnosed cases on TBLB were diagnosed by the BAL. Of 54 patients, 43 (79.6%) were infective, 9 (16.6%) were having non-infective etiology, and 2 (3.7%) cases were having combined etiology (infective + non-infective). The distribution of final diagnosis on BAL and TBLB is depicted in Table 3. As evident from Table 4, the most common microorganisms detected were mycobacterium tuberculosis (18.5%) and pseudomonas aeruginosa (18.5%).

Of 41 cases diagnosed as CAP on BAL, 36 cases (87.8%) had CAP on TBLB also and 5 cases (12.2%) did not have CAP on TBLB and were diagnosed only on BAL. Of 40 cases diagnosed as CAP on TBLB, 36 cases (90.0%) had CAP on BAL and 4 cases (10.0%) did not have CAP on BAL and were diagnosed only on TBLB. Of 13 cases without CAP on BAL, 4 cases (30.8%) had CAP on TBLB and 9 cases (69.2%) did not have CAP on TBLB. Of 14 cases without CAP on TBLB, 5 cases (35.7%) had CAP on BAL and 9 cases (64.3%) did not have CAP on BAL. The distribution of diagnosis of CAP by BAL was significantly associated with the diagnosis of CAP by TBLB ($p = 0.001$) with Cohen-kappa value of 0.556 (which is in the moderate range). There is a moderate statistically significant agreement between the diagnosis of CAP by BAL and TBLB in the study group (Table 5).

The sensitivity, specificity, PPV, NPV, and accuracy was 91.1, 100, 100, 30.8, and 92.6%, respectively, in the diagnosis of CAP on BAL, whereas the sensitivity, specificity, PPV, NPV, and accuracy was 88.9, 100, 100, 35.7, 90.7%, respectively, in diagnosis of CAP on TBLB (Table 6). The sensitivity, specificity, PPV, NPV and accuracy was 75.9, 100, 100, 100, 75.9%, respectively, in diagnosis of all the patients on BAL, whereas the sensitivity, specificity, PPV, NPV, and accuracy

Table 1: Demographic and clinical profile

Variables	*n (%)*
Age-group (years)	
<40	9 (16.6)
41–50	6 (11.1)
51–60	16 (29.6)
61–70	15 (27.8)
>70	8 (14.8)
Gender	
Male	40 (74.0)
Female	14 (26.0)
Comorbidity	
Nil	14 (25.9)
Hypertension	14 (25.9)
Diabetes mellitus	8 (14.8)
Hypertension + Diabetes mellitus	5 (9.3)
Hypothyroidism	3 (5.6)
Immunocompromised disease	11 (20.4)
Chronic lung disease	3 (5.6)
Other	10 (18.5)
Habits	
Nil	22 (40.7)
Tobacco chewing	3 (5.6)
Misri	3 (5.6)
Smoking	20 (37.0)
Alcohol consumption	2 (3.7)
Smoking + Alcohol consumption	4 (7.4)

Table 2: Outcome of the study population

Variables	*n (%)*
Duration of hospital stay (days)	
≤7	25 (46.3)
8–14	18 (33.3)
15–21	7 (13.0)
>21	4 (7.4)
Incidence of mortality	
Survived	49 (91.0)
Died	5 (9.0)

Table 3: Final diagnosis on BAL and TBLB in the study group

Final diagnosis	*BAL n (%)*	*TBLB n (%)*
Inconclusive	13 (24.0)	3 (5.6)
Typical organism	23 (42.6)	
Atypical mycobacteria	1 (1.9)	
Tuberculosis	10 (18.5)	9 (16.7)
Nocardiosis	3 (5.6)	3 (5.6)
PJP	2 (3.7)	2 (3.7)
Aspergillosis	2 (3.7)	3 (5.6)
NSC lung carcinoma		2 (3.7)
HSP		2 (3.7)
BOOP		1 (1.9)
Other		2 (3.7)
Adenocarcinoma of lung		4 (7.4)
Pneumonia		21 (38.8)
Mucormycosis		2 (3.7)
Total	54 (100.0)	54 (100.0)

BAL, bronchoalveloar lavage; BOOP, bronchiolitis obliterans organizing pneumonia; HSP, hypersensitivity pneumonitis; NSC, non-small cell; PJP, *pneumocystis jiroveci* pneumonia; TBLB, transbronchial lung biopsy

Table 4: Distribution of type of organisms isolated after performing BAL and TBLB

Type of organisms	*n (%)*
Acinetobacter baumanii	3 (5.6)
Klebsiella pneumoniae	9 (16.7)
Pseudomonas oryzihabitans	1 (1.9)
Pseudomonas aeruginosa	10 (18.5)
Atypical mycobacteria	1 (1.9)
Mycobacterium tuberculosis	10 (18.5)
Mucormycosis	2 (3.7)
Nocardia	3 (5.6)
Pneumocystis jiroveci	2 (3.7)
Aspergillus species	4 (7.4)
Non-microbial	9 (16.7)
Total	54 (100.0)

Table 5: Distribution of diagnosis of CAP according to BAL and TBLB

	CAP on TBLB			*Cohen–kappa*	
	Positive	*Negative*	*Total*		*p-value*
CAP on BAL	*n (%)*	*n (%)*	*n (%)*		
Positive	36 (87.8)	5 (12.2)	41 (100.0)	0.556	0.001
Negative	4 (30.8)	9 (69.2)	13 (100.0)		
Total	40 (74.1)	14 (25.9)	54 (100.0)		

was 94.4, 100, 100, 100, and 94.4%, respectively, in diagnosis of all the patients on TBLB (Table 7).

Discussion

The current study was conducted to evaluate the microbial, cytological, and histopathological analysis of BAL and TBLB in the diagnosis of CAP. Our study showed that diagnostic yield was 75.9% on BAL, 94.4% on TBLB, and 100% with combined use of both BAL and TBLB. The sensitivity of BAL and TBLB was 91.1 and 88.9%, respectively, in the diagnosis of CAP. El-Shabrawy M and EL-Sokkary RH reported that BAL culture and sensitivity was the maximum one.[12] Kim ES et al. stated that culture of BAL revealed decent sensitivity (80%) in finding bacterial pathogens in patients who did not show improvement in the first 3 days of treatment.[13] Griffiths MH et al. stated that the sensitivity for the diagnosis of BAL and TBLB was 90 and 56%, respectively.[10]

Table 6: Diagnostic efficacy indices of BAL and TBLB in the diagnosis of CAP

	Diagnostic efficacy indices (%)				
Procedure	*Sensitivity*	*Specificity*	*Positive predictive value*	*Negative predictive value*	*Accuracy*
BAL	91.1	100	100	30.8	92.6
TBLB	88.9	100	100	35.7	90.7

Table 7: Diagnostic efficacy indices of BAL and TBLB in the diagnosis of all patients

	Diagnostic efficacy indices (%)				
Procedure	*Sensitivity*	*Specificity*	*Positive predictive value*	*Negative predictive value*	*Accuracy*
BAL	75.9	100	100	100	75.9
TBLB	94.4	100	100	100	94.4

In this study, 43/54 (79.6%) patients had infective pathogen, such as *Mycobacterium tuberculosis* (18.5%), *Pseudomonas aeruginosa* (18.5%), *Klebsiella pneumoniae* (16.6%); 9 patients (16.6%) were having non-infective etiology; while 2 patients (3.7%) were having combined etiology; even rarer causes such as mucormycosis 2 (3.7%), nocardia 3 (5.6%), *Pneumocystis jiroveci* pneumonia 2 (3.7%), aspergillosis 4 (7.4%) that presented as necrotizing pneumonia were detected.

Griffiths MH et al. reported that the maximum pathogens isolated were *Pneumocystis carinii* (43 patients), whereas cytomegalovirus was detected three and one times by lavage and transbronchial biopsy, respectively.[10] El-Shabrawy M and EL-Sokkary RH reported that the most common cause of non-resolving pneumonia was bacterial pneumonia 113 (83.7%), whereas bronchogenic carcinoma and tuberculosis were detected in 13.3% and 4 (2.96%) patients, respectively. The study further stated that *Klebsiella pneumoniae* was the commonest isolate 29 (24.78%), whereas both *pseudomonas aeruginosa* and *streptococcus pneumonia* were detected in 23 isolates.[12]

Chaudhuri AD et al. reported that the most common cause of non-resolving pneumonia was bacterial pneumonias 32 (53%), whereas bronchogenic carcinoma, tuberculosis, and Wegener's granulomatosis were diagnosed in 16 (26.67%), 10 (16.67%), and 1 (1.67%) patient, respectively, but the diagnosis could not be done in one patient even though all the investigations were conducted. The study further stated that gram-negative bacilli and *staphylococcus aureus* were detected in 30/32 (93.75%) and 2 (6.25%) patients, respectively, who had bacterial pneumonia whereas *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, *Escherichia coli* and *Acinetobacter Baumannii* were found in 13,

11, 3 and 3 patients, respectively. The study further stated that of 16 cases of bronchogenic carcinoma, squamous cell cancer, adenocarcinoma and small cell variety was diagnosed in 10, 5, and 1 patient respectively; 7 (70%) patients of squamous cell carcinoma were detected by bronchoscopic biopsy. The study adds that the BAL fluid was positive in 40/56 (71.4%) patients; out of 40 patients, 31, 6, and 3 had pyogenic organisms, mycobacterium infection, and squamous cell cancer, respectively. Bronchoscopic biopsy detected non-specific inflammation, squamous cell cancer, small cell cancer, and tuberculosis in 46/56 (82.1%), 7 (12.5%), 1 (1.8%) and 2 (3.6%) patients, respectively.[14]

Kim ES et al. reported that positive BAL culture (>10,000 colonies) was observed in 18/340 (5.29%) patients, and 25 microbes were isolated at concentrations above the diagnostic threshold. Of 25 microbes isolated, 3, 4, 4, and 3 patients had polymicrobial infection, methicillin-resistant *Staphylococcus aureus*, *Acinetobacter baumannii*, and *Pseudomonas aeruginosa* infection, respectively.[13]

In this study, the majority of patient were aged between 51 and 70 years of age, with range 25–84 years and mean ± SD was 56.9 ± 13.5 years with 74% males; 14 (25.9%), 8 (14.8%), 5 (9.3%), and 3 (5.6%) patients were having hypertension, diabetes mellitus, hypertension + diabetes mellitus, chronic lung disease, respectively, whereas 20.4% patients were immunocompromised; 59.3 % patients were having habit of smoking, tobacco chewing or alcohol drinking with majority of them smoking implying that these patients were at more risk of development of CAP. These findings are supported by a systemic review of an observational research on risk factors for CAP in adult population conducted by Almirall J et al.[15] Almirall J et al. stated that there is a convincing evidence of age, tobacco smoking, environmental exposures, poor nutritional status, chronic bronchitis/chronic obstructive pulmonary disease (COPD), bronchial asthma, diabetes mellitus, coronary heart disease, history of CAP (in the past 1 or 2 years), bad oral health, immunosuppressive treatment, oral steroids, and the use of proton pump inhibitors or H2 antagonists as risk factors for CAP in adult population. Cigarette smoking has a direct and independent effect on the risk of pneumonia. Cigarette smoking also leads to COPD, which is a well-documented risk factor for CAP. Furthermore, COPD is more common in men because women smoke less as compared to men. Hence, men are at more risk developing CAP.[15]

The strength of our study was that eventual diagnosis was obtained in 100% of patients, with combined use of BAL and TBLB. The limitation of the research was the study was conducted in a single center of a tertiary care hospital with a small sample size. Hence, the results of the study cannot be generalized to larger population. It is recommended to conduct the studies in different centers to corroborate the research findings described in this manuscript.

Conclusion

The diagnostic yield was 75.9% on BAL, 94.4% on TBLB and 100% with combined use of both BAL and TBLB. The sensitivity of BAL and TBLB was 91.1 and 88.9%, respectively, in the diagnosis of CAP. In this study, 43/54 (79.6%) patients had infective pathogen, such as *Mycobacterium tuberculosis* (18.5%), *Pseudomonas aeruginosa* (18.5%), *Klebsiella pneumoniae* (16.6%); and rarer causes like mucormycosis 2 (3.7%), nocardia 3 (5.6%), *Pneumocystis jiroveci* pneumonia 2 (3.7%), and aspergillosis 4 (7.4) which presented as necrotizing pneumonia were also identified.

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