INTRODUCTION

Bronchoalveolar lavage (BAL) has been used to evaluate patients with suspected interstitial lung disease (ILD) to identify the specific type. The advent of high-resolution computed tomography (HRCT) has reduced the clinical utility of BAL. HRCT can noninvasively identify specific imaging patterns that may be associated with certain forms of ILD. This has greatly improved the clinician's ability over the past decade to narrow down the differential diagnosis.\textsuperscript{1,2} Albeit the usefulness of HRCT, diagnostic sampling using BAL is also performed when there is an ongoing clinical suspicion of ILD despite a normal HRCT. This work has utilized the recommendations of the American Thoracic Society (ATS) to optimize BAL and the findings have been associated with clinical examination and HRCT to precisely narrow down the cause of ILD.

ABSTRACT

**Background:** Bronchoalveolar lavage (BAL) has gained acceptance for diagnosis of Interstitial lung disease (ILD). The advent of high-resolution computed tomography (HRCT) has reduced the clinical utility of BAL. This work has utilized the recommendations of the American Thoracic Society (ATS) to optimize BAL and the findings have been associated with clinical examination and HRCT to precisely narrow down the cause of ILD. **Materials and Methods:** BAL was performed on ILD suspects at the target site chosen based on HRCT. The procedure, transport, processing, and analysis of BAL fluid were performed as per the ATS guidelines. The clinical data, HRCT findings and BAL report were used to narrow down the diagnosis of ILD. The statistical analysis was performed to assess the significance. **Results:** The BAL procedure was optimized as per the recommendations of the ATS. In a cohort of 50 patients, Idiopathic pulmonary fibrosis, (8) hypersensitivity pneumonitis, (17) connective tissue disorder, (9) sarcoidosis, (3) pneumoconiosis, (5) acute respiratory distress syndrome, (2) eosinophilic lung disease (2) and lymphangitic carcinomatosa, (2) aspiration bronchiolitis (1) and pulmonary histiocytosis (1) were diagnosed. Statistically significant variation in differential counts was found in different ILDs. The different ILDs were classified based on the criteria described by the ATS. **Clinical Significance:** BAL along with clinical and HRCT findings improved the diagnostic accuracy by incorporating, the acute or chronic nature of the disease and the cause for acute exacerbation, which helped in the better management of ILDs.

**Key Words:** ATS recommendations, bronchoalveolar lavage, Interstitial lung diseases
evaluation of patients presenting with suspected ILD, BAL cellular analysis may be a useful adjunct in the diagnostic evaluation of individuals to confirm the HRCT findings and also to fine-tune their clinical diagnosis for better management of ILD patients.

BAL samples the cellular and acellular components of distal bronchioles and gas exchange units. BAL analysis, by itself, may not be diagnostic, but BAL cell pattern results may support a diagnosis and/or narrow down the differential diagnosis when considered in the context of medical history, physical examination, and radiologic findings.[3] The usefulness of BAL cell findings is hampered by its poor sensitivity and specificity.[4] In addition, a normal BAL differential cell profile does not exclude the presence of microscopic abnormalities in lung tissue. The clinical utility of BAL in identifying the cause of ILD is proved, provided the technique is performed correctly, BAL fluid handled and processed properly. Recently, the American Thoracic Society (ATS) clinical practice guidelines have provided a comprehensive, conceptually balanced and evidence-based perspective on the clinical utility of BAL cellular analysis for the evaluation of suspected ILD.[5] These guidelines will increase the utility of BAL in the diagnostic evaluation of ILD and promote the use of BAL in clinical utility of ILD so that future guidelines will be based on high-quality evidence. In this work, the recommendations put forth by the ATS have been utilized to optimize the BAL procedure and associated the findings with different clinical entities of ILD including HRCT. This may facilitate future clinical studies in patients with suspected ILD, which investigate potential biomarkers in BAL that may predict prognosis and response to therapeutic interventions for ILD.

MATERIALS AND METHODS

This study was approved by the Institutional Ethics Committee and the guidelines of the Declaration of Helsinki were followed. Informed consent was obtained from patients before the invasive procedure. ILD patients were recruited based on the clinical and radiological evaluation.

Inclusion criteria

Patients above the age of 18 years, clinical and HRCT proven ILD patients tolerable to the BAL procedure. Pediatric patients, pregnant women, ILD patients with bleeding disorders and those with cardio-respiratory instability were excluded from the study. Patients were subjected to routine blood investigations including HIV testing, cardiac and rheumatological evaluations. Malignancies and presence of infection were excluded by standard diagnostic modalities. After obtaining cardiac fitness for the BAL procedure, patients whose respiratory status was adequate, were subjected to the BAL procedure as per the ATS guidelines.[5] The clinical data, HRCT findings and BAL report were used to narrow down the diagnosis of ILD.

Statistical analysis

Nonparametric analysis was performed after finding the median values of different cell counts obtained from the fluid analysis. The overall significance of the cell counts between different ILDs was assessed using SPSS version 13 (SPSS, Chicago, IL, USA) and \( P < 0.05 \) was considered as significant.

RESULTS

Fifty consecutive ILD patients with classical HRCT findings were recruited for the study after obtaining informed consent. Clinically suspected ILD patients were subjected to HRCT and based on the HRCT findings, BAL was performed after selecting the site for fluid collection in the lungs. The procedure, transport, processing and analysis of BAL fluid were optimized as per the ATS guidelines. The patients were segregated based on the ATS classification. The segregation of the cohort as per the clinical diagnosis is as follows (number of patients is given in brackets): Idiopathic pulmonary fibrosis (8), hypersensitivity pneumonitis (17), connective tissue disorder (9), sarcoidosis (3), pneumoconiosis (5), ARDS (2), eosinophilic lung disease (2) and lymphangitic carcinomatosa (2), aspiration bronchiolitis (1) and pulmonary histiocytosis (1). The demographic data and the findings are listed in Table 1. Radiation pneumonitis was seen in the 6th decade, IPF and CHP in the 5th decade, ELD, CTD, SAR and SIL were noticed in the 4th decade of life. The average duration of the disease was 3.1 years, 14.3 years and 1.5 years for IPF, CHP and CTD, respectively.

Table 1: Demographic, interstitial lung disease and bronchoalveolar lavage cell count analysis

| AAD     | Male (%) | Duration mean years | Diagnosis | TCC | AM | LY | NE | EOS | HIS |
|---------|----------|---------------------|-----------|-----|----|----|----|-----|-----|
| 51.2    | 88.8     | 3.1                 | IPF       | 90  | 82 | 15 | 3  | 0   | 0   |
| 53.2    | 82.3     | 14.3                | CHP       | 95  | 50 | 39 | 10 | 0   | 0   |
| 44.4    | 22.2     | 1.5                 | CTD       | 101 | 57 | 29 | 19 | 0   | 0   |
| 44.0    | 0        | -                   | SAR       | 110 | 45 | 33 | 22 | 0   | 0   |
| 46.8    | 100      | -                   | SIL       | 103 | 71 | 20 | 9  | 0   | 0   |
| 52      | 50       | -                   | ARDS      | 340 | 38 | 25 | 37 | 0   | 0   |
| 40.5    | 0        | 3                   | ELD       | 90  | 48 | 17 | 7  | 29  | 0   |
| 63      | 0        | 45 days             | RP        | 100 | 59 | 25 | 16 | 0   | 0   |
| 20      | 0        | 2                   | AB        | 96  | 54 | 12 | 32 | 0   | 0   |
| 49      | 100      | 180 days            | PH        | 100 | 0  | 10 | 0  | 0   | 90  |

AAD: Age at diagnosis, TCC: Total cell count, AM: Alveolar macrophages, LY: Lymphocytes, NE: Neutrophils, EOS: Eosinophils, HIS: Histocytes, NC: Normal Control, IPF: Idiopathic Pulmonary Fibrosis, CHP: Chronic Hypersensitivity Pneumonitis, CTD: Connective Tissue Disorder, SAR: Sarcoidosis, SIL: Silicosis, ARDS: Acute Respiratory Distress Syndrome, ELD: Eosinophilic Lung Disease, LC: Lymphangitic Carcinoma, AB: Aspiration Bronchiolitis, PH: Pulmonary Histiocytosis.
The lymphocytes in lung secretions were significantly high in IPF, CHP, CTD and SAR, while the percentage of neutrophils were significantly high in all the subgroups of ILDs noted in the cohort in comparison to normal values.

**Idiopathic pulmonary fibrosis**

Eight patients were diagnosed with IPF based on clinical evaluation, pulmonary function test (restrictive pattern), and HRCT findings (subpleural/basal reticulation and honeycomb appearance). The cell cytology of BAL on seven IPF patients revealed a lymphocyte count range of 25% to 38% and neutrophil count range of 12% to 52%. For those with a neutrophil count range <50%, a diagnosis of bilateral sub-acute IPF with bronchitis probably with superadded infection was made. A diagnosis of bilateral acute IPF with bronchitis and suppurative infection was made in one patient with a neutrophil count above 50%.

In patient 7, as the lymphocyte count was 70%, a diagnosis of bilateral sub-acute exacerbation of nonspecific ILD with bronchitis probably associated with superadded infection was high, the analysis was forbidden due to sub-optimal sample.

**Chronic hypersensitivity pneumonitis**

Out of 17 patients diagnosed with CHP, patient 11 was not analyzed due to sub-optimal quality identified based on REC. In the rest of the samples, the lymphocyte count range was 26–55%, and the neutrophil count was in the range of 5–20%. Based on the cellular count, a diagnosis of bilateral sub-acute exacerbation of CHP with bronchitis probably associated with superadded infection was made in all these patients. In addition to the above findings, patient 10 had 3% eosinophils, which redefined the diagnosis as bilateral sub-acute exacerbation of CHP with allergic bronchitis probably associated with superadded infection.

**Connective tissue disorder**

The lymphocyte range was 8–70% while the neutrophil count was in the range of 8–65% in nine patients. In patient 23, as the lymphocyte count was 70%, a diagnosis of sub-acute exacerbation of nonspecific ILD with bronchitis probably associated with superadded infection was made. In patient 24, with systemic rheumatoid arthritis and a neutrophil count above 50% in the BAL cellular pattern, the diagnosis was refined as bilateral acute exacerbation of rheumatoid arthritis induced ILD with bronchitis and suppurative infection. In the rest of the patients, the diagnosis was defined as bilateral sub-acute rheumatoid arthritis induced ILD with bronchitis probably associated with superadded infection or bilateral sub-acute systemic scleroderma induced ILD with bronchitis probably associated with superadded infection based on their systemic disease.

**Eosinophilic lung disease**

Apart from the routine lymphocyte and neutrophil count, eosinophil count of more than 25% was virtually diagnostic of acute or chronic eosinophilic pneumonia.

**Pulmonary histiocytosis**

Predominance of histiocytosis BAL fluid was able to narrow down this diagnosis.

**Sarcoidosis**

In three patients with sarcoidosis, the lymphocyte and neutrophil count range was 28–32% and 10–45%, respectively. Based on the BAL findings, the previous diagnosis was refined as bilateral sub-acute sarcoidosis induced ILD with bronchitis probably associated with superadded infection.

**Silicosis**

The five patients were diagnosed with SIL induced lung injury based on HRCT findings; the BAL report refined the diagnosis enumerating the acute/chronic nature of the disease.

**ARDS, radiation pneumonitis and aspiration bronchiolitis:** These diseases were diagnosed based on the clinical history and examination and the role of BAL in defining the diagnosis was limited.

In succinct, BAL findings were able to clinch the diagnosis in eosinophilic pneumonia and pulmonary histiocytosis, whereas it refined the diagnosis of IPF and CHP. On the other hand, the role of BAL findings in sarcoidosis and SIL was limited as HRCT had precisely helped to diagnose the disease based on the image pattern. BAL had no role to play in the diagnosis of ARDS, radiation pneumonitis and aspiration bronchiolitis as the diagnosis is largely based on the clinical history and evaluation.

**DISCUSSION**

Usefulness of a clinical diagnostic test is graded based on its sensitivity, specificity, invasiveness, reproducibility, and its contribution to the diagnosis of the disease. Based on these factors, new diagnostic tests for disease are invented and the old test wanes with time. Interestingly, as the pathogenesis of disease ravel with time, there may be a need for multiple clinical tests to make a precise diagnosis and to improve the management strategy. Under these situations, it may be difficult to conceive that an old test which had been used in the past for a particular disease would have new potential uses in modern medicine.

BAL has gained widespread acceptance as a procedure that can be performed safely to retrieve respiratory secretions for the examination of cellular and acellular components for both diagnostic purposes. BAL was perceived to hold a great potential for diagnosis and management of ILD. It eventually became clear, that although BAL nucleated immune cell patterns often had characteristics that were highly consistent with various forms of ILD, BAL cell counts and differentials, lymphocyte subsets, or soluble components could not be relied on to make a confident diagnosis for many specific forms of ILD if used as a standalone diagnostic test. The evaluation of ILDs...
based on BAL findings was typically nonspecific, being consistent with or suggestive of a given condition, rather than pathognomonic. The BAL data had considerable variability and the number of potential diseases was far greater than the number of safely discernible cellular patterns. Only in rare instances, the data led to a unique conclusion while in a majority of cases, BAL cell differentials could render certain diagnoses and exclude all others with some probability. This uncertainty, in combination with the differences in clinical setting and experience, resulted in different opinions about the diagnostic value of BAL among the clinicians.

In the early 1990s, HRCT came into widespread clinical use. As HRCT imaging patterns were consistent with specific forms of ILD such as IPF or sarcoidosis, the likelihood of making a diagnosis was high. Despite the acceptance of obtaining an HRCT scan from patients with ILD during the initial stages, many patients with new-onset of ILD may not have the characteristic patterns that allow a diagnosis to be made with a high level of confidence by HRCT imaging alone. However, when clinical information and HRCT findings were combined with BAL fluid analysis, confident diagnoses may emerge that obviate the need for surgical lung biopsy. Although the BAL cell pattern can provide useful information about a specific ILD diagnosis, this would be possible only if an appropriate technique is used by the bronchoscopist to obtain the fluid; the differential cell count is performed according to good clinical laboratory practice by personnel with adequate experience in BAL cytological analysis and interpreted by an expert familiar with the diverse spectrum of specific forms of ILD.

With this in mind, this study utilized the recommendations and guidelines of the ATS on the use of BAL in the diagnosis and management of patients with suspected ILD. Based on the cellular pattern obtained, it was able to fit the differential diagnosis of 47 patients within the classification provided by the ATS. Inappropriate BAL procedure was observed in rest of the three patients. Later, diagnosis of different ILDs were made based on the clinical examination, HRCT findings, and the BAL cell pattern separately. All the three modes of assessment landed up in a set of differential diagnosis for each assessment. When a clinical diagnosis was combined with HRCT, the differential diagnosis was narrowed down to a minimum of two diseases. However, BAL cellular pattern along with the clinical examination and HRCT findings not only narrowed down the type of ILD but also enhanced the diagnosis for a better management strategy. The enhancement in the diagnosis included stability of the disease, acute or chronic nature of the disease and probable cause for acute exacerbation. This leaves the physician to take an appropriate decision to treat the cause of acute exacerbation along with the primary etiology or to treat the primary cause alone. Thus, this multiple assessment strategy enabled to treat patients appropriately with much more precision and accuracy.

In patient 1, an IPF suspect, HRCT had provided four differential diagnoses of IPF, CHP, asbestososis, sarcoidosis and CTD based on honeycomb appearance. The clinical findings and BAL analysis suggested four differential diagnoses namely IPF, nonspecific interstitial lung disease, acute lung disease and suppurative infection. Combining the clinical, HRCT and BAL findings, the diagnosis was refined as acute exacerbation of IPF with bronchitis probably associated with superadded infection. This had helped the clinician to treat the infection to control the acute episode. In patient 8, HRCT listed the differential diagnosis similar to that of patient 1 based on honeycomb appearance. However, BAL clearly demonstrated the predominance of histiocytes in the lung secretion to narrow down the diagnosis as pulmonary histiocytosis [Table 2]. This changed the modality of treatment in this patient.

In patient 9 with a clinical diagnosis as ILD, HRCT revealed bilateral upper lobe fibrosis with traction bronchiectasis. Adding BAL input, redefined the diagnosis as sub-acute exacerbation of CHP associated with noninfectious bronchitis based on the lymphocyte and neutrophil counts. On the other hand, patient 12 had a neutrophil count more than 50% in the cellular pattern that gave a diagnosis of acute exacerbation of CHP with bronchitis and suppurative infection. In eosinophilic pneumonitis, the BAL played a very important role in assisting clinical and HRCT findings to clinch the diagnosis. In some of the ILDs such as the sarcoidosis, SIL, radiation pneumonitis, ARDS and ILD associated with collagen vascular diseases, HRCT stands as an important test along with clinical examination in determining the diagnosis. In all these diseases, the BAL was helpful to predict the acute/sub-acute or chronic nature of the disease and the association of infection.

**CONCLUSION**

We conclude that BAL performed as per the guidelines

| Table 2: Diagnosis of interstitial lung disease based on HRCT alone; clinical diagnosis and BAL; HRCT, clinical diagnosis and BAL |
|--------------------------------------------------|
| **Patient** | **HRCT** | **CD and BAL** | **IPF; CHP; Asbestososis; SAR; CTD** |
|------------|----------|----------------|-------------------------------------|
| **Patient 1** | HRCT | CD and BAL | Acute Exacerbation of Idiopathic Pulmonary Fibrosis with Bronchitis |
| **Patient 8** | HRCT | CD and BAL | IPF; Pulmonary Langerhan Cell Histiocytosis |
| **Patient 9** | HRCT | CD and BAL | Fibrosis with Traction Bronchiectasis |

HRCT: High Resolution Computed Tomography, CD: Clinical Diagnosis, BAL: Bronchoalveolar Lavage, IPF: Idiopathic Pulmonary Fibrosis, CHP: Chronic Hypersensitivity Pneumonitis, SAR: Sarcoidosis, CTD: Connective Tissue Disease

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of the ATS may act as an important test along with the clinical and HRCT findings for a proper diagnosis in some ILDs, whereas in others, HRCT was found to be more successful in predicting the diagnosis. BAL assists in predicting the acute/chronic nature of the disease and gives a hint on the superadded infection status that would help in proper management. Thus, in addition to routine clinical evaluation and HRCT, BAL should be employed more routinely in the evaluation of patients with ILD.

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Conflicts of interest
There are no conflicts of interest.

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