The clinical utility of bronchoalveolar lavage in interstitial lung disease – is it really useful?

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Bronchoalveolar lavage (BAL) can be a very useful tool in the diagnosis of interstitial lung disease, but BAL must be performed properly and the retrieved BAL fluid adequately processed and analyzed to allow accurate conclusions to be drawn from BAL analysis. A differential cell count of nucleated immune cells can show cell patterns that suggest or support certain diagnoses, and other testing (stains and cultures for infectious pathogens, malignant cell cytology) can be performed on BAL fluid that can also aid in diagnosis. When combined with the results of a careful history, physical examination, thoracic imaging, and other pertinent laboratory testing, the BAL analysis may allow a confident diagnosis of a specific interstitial lung disease to be made without proceeding to more invasive testing (e.g., surgical lung biopsy) that is associated with increased risk of complications.

Bronchoalveolar lavage (BAL) was introduced into the clinical arena in the mid-1980s and it is now routinely used as a tool to evaluate patients with acute respiratory compromise, suspected pulmonary infection or diffuse parenchymal lung disease [1]. BAL can be easily and safely performed, and analysis of BAL fluid can provide information that is useful in determining the etiology and ultimate diagnosis of the bilateral parenchymal infiltrates that patients with suspected interstitial lung disease (ILD) usually have when they seek medical care [2–4]. Although specific types of ILD cannot usually be diagnosed solely on the basis of BAL analysis, BAL nucleated immune cell analysis, when combined with imaging and other clinical data, may provide enough information such that a surgical biopsy may not be required as part of the diagnostic evaluation.

What are essential aspects of the BAL procedure?

Clinicians should adequately evaluate the patient prior to performing bronchoscopy and BAL to ensure that the procedure can be performed safely [4]. If the disease is diffuse, the right middle lobe or lingula of the left upper lobe can be targeted, as the bronchoscope can be readily wedged in these bronchi and fluid retrieval from these areas tends to be better than from other lung regions. The recently published American Thoracic Society clinical practice guideline suggests that a high-resolution computed tomography should be performed within 6 weeks of the procedure so that optimal sites (which may not be in the right middle lobe or lingula) for performing the BAL can be detected and chosen [4].

BAL should be performed with the distal end of the bronchoscope in a wedge position in a segmental bronchus to prevent the instilled isotonic saline from getting dispersed into nontargeted regions, which will not only decrease the amount of retrieved BAL fluid but also cause cough and patient discomfort; retrieval of the instilled saline may be considerably or totally compromised if a wedge position is not maintained. Using a hand-held syringe to instill and withdraw lavage aliquots allows adjustment of negative pressure such that significant airway collapse can be avoided. Aliquot

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size used by various investigators has ranged from 20 to 60 ml with total instilled saline volume ranging from 100 to 300 ml. It is suggested that if the total volume of unretrievable fluid in a lavaged segment exceeds 100 cc, the instillation of additional fluid aliquots into that segment should be avoided. The retrieved BAL aliquots can be pooled, and the percentage of total instilled BAL fluid that should be retrieved to provide an adequate sample should be 30% or greater.

What are the key aspects of performing BAL analysis?

The appearance of the retrieved BAL fluid, and especially, the BAL cell differential counts can provide useful diagnostic information if abnormal patterns are recognized and correctly interpreted, but BAL fluid processing and specimen preparation must be done by well-trained personnel who are familiar with BAL protocols with proper adherence to good clinical laboratory practice guidelines [4]. BAL fluid should be promptly transported to the clinical laboratory where processing and analysis will be performed. Total cell counts can be easily obtained, and the cytospin method is typically used to place BAL cells on glass slides for staining and determination of differential cell count percentages. The identification of BAL nucleated immune cell types should be performed by laboratory personnel who are proficient in their ability to recognize the morphological features of the immune cell types (including plasma cells and mast cells) and other cells (e.g., epithelial cells), and at least 300 or more cells should be counted on a slide to give an accurate differential enumeration of specific cell types. Slides can be examined by a cytopathologist if malignancy is a consideration, and tests to detect potential respiratory pathogens should be performed as appropriate. Lymphocyte subset determinations (CD4 and CD8 T lymphocytes) can be performed via monoclonal antibody staining and flow cytometric analysis, but routine determination of BAL CD4/CD8 ratios has limited utility and is not recommended [4]. Immunohistochemistry with appropriate antibody staining may be useful to identify lymphocyte clonal proliferation or Langerhans cells in certain situations.

What is the role of BAL in the diagnosis of ILD?

If BAL is properly performed, processed and analyzed, the information obtained can be very useful in the diagnosis of suspected ILD. BAL nucleated immune cell patterns that deviate from that observed in normal individuals (80–90% alveolar macrophages; 5–15% lymphocytes; ≤3% neutrophils; ≤1% eosinophils) are indicative of an infiltrative/inflammatory process that has perturbed the lung airways and/or interstitium. When imaging supports a diffuse/interstitial process, significant increases in differential percentages of lymphocytes, eosinophils or neutrophils increase suspicion for specific forms of ILD. However, increased percentages of more than one of these cell types may be detected (e.g., lymphocytes and neutrophils in hypersensitivity pneumonitis [HP], sarcoidosis or organizing pneumonia; neutrophils and eosinophils in usual interstitial pneumonia). When expertly examined BAL cell differential counts and other BAL characteristics are combined with clinical and imaging data, information obtained from the combined data may be adequate to provide a confident, specific diagnosis. However, cell patterns may be obtained that are not typical for a specific ILD diagnosis, or BAL cell analysis may show little or no change from the profile that is typically found in normal subjects despite the presence of an ILD. Additionally, abnormal BAL cell profiles may be present when various disorders of airways are present such as bronchiolitis, eosinophilic bronchitis, bronchiectasis or asthma.

A BAL lymphocytosis with BAL differential count >25% is very consistent with a granulomatous pneumonitis (sarcoidosis or HP) but can be seen with other entities such as a drug reaction or cellular nonspecific interstitial pneumonia. An extreme increase in the BAL eosinophil percentage (≥25%) is strongly supportive of eosinophilic pneumonia as a diagnosis, and prominent BAL neutrophilia suggests a diagnosis of infection or acute/subacute lung injury. Analysis of BAL cell differentials from a large cohort of patients by Welker *et al.* [5] suggested that BAL differential cell counts were most useful in the diagnosis of relatively common ILD diagnoses such as sarcoidosis, and a more recent analysis of BAL findings from patients with a suspected diagnosis of usual interstitial pneumonia-idiopathic pulmonary fibrosis (IPF) stated that a high BAL lymphocyte differential count (>30%) suggests that the diagnosis is likely inaccurate and that such patients have another diagnosis such as HP [6].

Additional information can be obtained from the appearance of the retrieved BAL fluid or analysis of other BAL components that can implicate a specific ILD diagnosis (e.g., diffuse alveolar hemorrhage or pulmonary alveolar proteinosis) or indicate an alternative, non-ILD diagnosis such as infection or neoplasm. Examination of an appropriately stained BAL cell slide preparation by a cytopathologist may reveal the presence of a malignancy (e.g., lymphangitic carcinoma or lymphoma) that can have an ILD-like appearance on thoracic imaging and special stains and/or cultures may detect the presence of an infection (e.g., histoplasmosis or mycobacterial infection).

What is the future of BAL for diagnosis & treatment of ILD?

As the field of genomics evolves, BAL cell gene expression patterns and BAL fluid proteomic patterns may prove useful to differentiate among specific forms of ILD that may have a similar clinical presentation and imaging pattern (e.g., HP vs IPF). Additionally, such analyses may facilitate choosing effective therapies for specific ILD, monitoring disease activity and assessing the effect of pharmacological therapies. Lastly, because gastroesophageal reflux and aspiration likely play a significant role in some ILDs (e.g., IPF, CTD-ILD) [7], detection of pepsin and/or bile acid in BAL fluid may prove to be a useful marker of gastroesophageal reflux with aspiration and facilitate clinical decision-making such as whether to perform antireflux surgery.

Conclusion

BAL by itself is not likely to provide a specific ILD diagnosis, but it can be performed quite safely. Patients who are suspected

to have ILD typically undergo a comprehensive clinical evaluation to determine whether a specific ILD is truly present and to identify the specific form of ILD with an acceptable degree of confidence [8]. Adequate imaging with high-resolution computed tomography of the thorax may provide a confident diagnosis when combined with other clinical information, but invasive testing may be required to achieve a confident diagnosis and adequately characterize the disease. When combined with other clinical data and imaging, BAL findings can often help secure a confident diagnosis and may obviate the need to proceed to the more invasive procedure of surgical lung biopsy, which is associated with significantly increased risk of morbidity and mortality [9].

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