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*by* Yolanda Handayani

**Submission date:** 17-Oct-2023 01:18PM (UTC+1100)
**Submission ID:** 2198163003
**File name:** UI_dr._Prasenohadi_intervensi.docx (2.75M)
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# Bronchoalveolar Lavage (BAL) in Pulmonary Alveolar Proteinosis and Sarcoidosis

**Prasenohadi***

Department of Pulmonology and Respiratory Medicine Faculty of Medicine, Universitas Indonesia, Persahabatan Hospital, Jakarta

**ABSTRACT**

Bronchoalveolar lavage (BAL) is one of minimal invasive procedure using flexible fiber optic bronchoscopy guidance which safe, easily performed, and well tolerated procedure. Bronchoalveolar lavage procedure is important to diagnose or differential diagnosis patient with clinical appearance and radiological finding not specific. Mechanism related to lung disorder such as inflammation, fibrosis, and abnormal material could be obtained by BAL fluid. Non infection lung disorder such as pulmonary alveolar proteinosis (PAP) and sarcoidosis may be diagnosed by BAL. BAL in non-infection lung disease has diagnostic and therapeutic function. As diagnostic function, BAL could be a tool to obtain lower respiratory tract sample and lavage from respiratory track could be therapeutic function of BAL.

**Keywords**: bronchoalveolar lavage, pulmonary alveolar proteinosis, sarcoidosis.

*Correspondence: Prasenohadi - praseno@gmail.com

## INTRODUCTION

Bronchoalveolar lavage (BAL) or bronchoalveolar lavage was first introduced during clinical practice in 1974 as a diagnostic tool for lung diseases.[1] Since then, the use of BAL with the guidance of flexible fiberoptic bronchoscopy (FOB) has been widely used as a diagnostic tool for various lung diseases, especially in interstitial lung diseases. BAL is performed with the help of FOB to sample the lower airway by rinsing the bronchoalveolar segment.[2] Therefore, the development of BAL is inseparable from the invention of FOB in 1960, which has safety and convenience in the visualization of lesions and bronchial biopsy, elbow and bronchial rinse for sampling the diagnosis of lung disease.[3]

BAL is a minimally invasive procedure using FOB guidance that is safe and easy to operate and well tolerated by patients.[4] Samples obtained from BAL are taken from a larger area than transbronchial biopsies so that they can provide additional information to support patient diagnosis and have advantages over histopathology biopsies.[5] BAL samples reflect pathological changes associated with elements of the lung parenchyma and can therefore be used as a diagnostic tool.[6] This review will discuss the use of BAL in non-infectious lung diseases focusing on pulmonary alveolar proteinosis (PAP) and sarcoidosis.

## BRONCHOALVEOLAR LAVAGE (BAL)

BAL is the collection of lower airway samples by instillation of sterile physiological fluid into the lung subsegment followed by suction and collection of the instillation fluid for analysis. BAL is performed using FOB guidance with topical anesthesia to prevent coughing. In addition, BAL can also be performed under general anesthesia and can be performed in patients with assisted ventilation via rigid bronchoscopy or endotracheal tube.[5] The total volume of fluid instilled during BAL should be at least 100 mL but not more than 300 mL, divided into three to five aliquots that are withdrawn per instillation. To obtain a good sample, the total volume of recalled fluid should be more than 30% of the total instilled fluid.[7] Through this technique, cells, inhaled particles, infectious organisms and lower airway solutes as well as alveoli epithelial cells can be retrieved. Information such as immunology, inflammation and infectious processes occurring in the alveoli can be found in BAL.[8]

### Indications, contraindications and complications of BAL

Airway symptoms and nonspecific radiological findings and clinical symptoms suggestive of a diagnosis of interstitial lung disease (ILD) are indications for BAL.[9] In addition, BAL is also performed in patients with normal thoracic images accompanied by clinical abnormalities and pulmonary function tests suggestive of diffuse lung disease. In patients with unexplained respiratory symptoms, normal BAL findings may rule out the diagnosis of ILD. Clinicians need to perform BAL as additional and confirmatory information in establishing a diagnosis based on the findings of high resolution computed tomography (HCRT) that cannot establish a diagnosis or when confirming additional information and confirming or ruling out a diagnosis. However, BAL cannot be a single diagnostic tool so it must be combined with clinical findings, laboratory examinations, and HRCT.[5,8]

The absolute contraindications for performing BAL are the same as bronchoscopy, such as cardiac arrhythmias and cervical disorders. Relative contraindications for BAL include uncooperative patients, forced expiratory volume in the first second ($VEP_1$) less than one liter, asthma with moderate airway obstruction, hypercapnia, hypoxemia that

cannot be corrected to $PaO_2$ 75 mmHg or $O_2$ saturation more than 90% with $O_2$ therapy, cardiac arrhythmia, myocardial infarction in the last 6 weeks, unresolved bleeding, and unstable hemodynamics.[10] In general, BAL is well tolerated by patients. However, some of the complications that occur are similar to those that occur with FOB. A minor complication that can occur after BAL is fever. This complication can be reduced by keeping the volume of BAL instillation less than 150 mL.[5] The fever that occurs after BAL may disappear without treatment within 24 hours. In patients with interstitial lung disease, less than 5% of patients undergoing BAL experience minor complications such as postbronchoscopy fever, pneumonitis, bleeding, and bronchospasm.[7]

## USEFULNESS OF BAL IN NON-INFECTIOUS LUNG DISEASES

The usefulness of BAL in diagnosing non-infectious lung diseases such as ILD is still a challenge, but BAL can be a definitive diagnostic tool if the results obtained are consistent with clinical findings and radiological data. The morphology of BAL fluid provides important information for diagnosing ILD. If the BAL fluid appears very cloudy or milky light brown or beige in color and there are white clots deposited at the bottom of the container, the diagnosis is most likely PAP. Lymphocyte subset analysis of BAL fluid provides important information when cell type analysis shows a lymphocyte cell presentation of ≥15%. An increase in CD4 and decrease in CD8 along with an increase in the ratio between CD4 and CD8 counts leads to the diagnosis of sarcoidosis when supported by appropriate clinical appearance and radiological features.[2] In addition to being useful for diagnosis, BAL is also useful as a therapy in PAP by modifying whole lung rinses.[11]

### Pulmonary Alveolar Proteinosis

PAP is a rare disease characterized by an imbalance in pulmonary surfactant homeostasis and accumulation of lipoprotein material in the alveoli. There are three classifications of PAP: primary PAP (autoimmune and hereditary), secondary PAP (quantitative and/or qualitative destruction of macrophages in the alveoli) and unqualified PAP (neither of the previous criteria). Factors that play a role in the pathogenesis of PAP resulting in progressive filling of the alveoli include lipoproteins and surfactant.[12,13] Surfactant consists of a mixture of 10% protein surfactants (SP) such as SP-A, SP-B, SP-C and SP-D and 90% lipids mainly phospholipids secreted by type II pneumocytes.[14]

Surfactant functions to maintain the lung by forming a layer between air and fluid on the surface of the alveoli, reducing pressure and preventing the alveoli from collapsing. The amount of surfactant is regulated by the balance of secretion and clearance of type II pneumocytes and alveoli macrophages. Granulocyte macrophages-colony stimulating factor (GM-CSF) is known to be key in regulating surfactant catabolism in alveoli macrophages. Research into the occurrence of PAP has been demonstrated in experimental mice that lack the GM-CSF gene. This underlying mechanism leads to impaired surfactant clearance and is classified as primary PAP while secondary PAP is associated with underlying disease that causes disruption of alveolar macrophage function.[14,15]

BAL fluid analysis can be used to confirm PAP. Macroscopically, a milky white fluid is seen due to the accumulation of surfactant derivatives such as phospholipid components and proteins in the alveoli.[8] Examination of BAL fluid using a microscope shows that the cell pattern shows an increase in lymphocytes, neutrophils and eosinophils.[16] The macrophage picture is fatty and there is sediment so that the appearance looks cloudy with May-Grunwald-Giemsa

(MGG) staining. The cytology of BAL fluid obtained in PAP patients is positive for Periodic Acid-Schiff (PAS) and oil-red-O staining.[14] Ultrastructural examination using electron microscopy of BAL fluid found type II pneumocyte cells containing a circular layer structure and some containing osmophilic dense nuclei and surrounded by protein debris.[12,17] The discovery of GM-CSF neutralizing antibodies in serum and BAL fluid indicates this disease is an autoimmune process.[18]

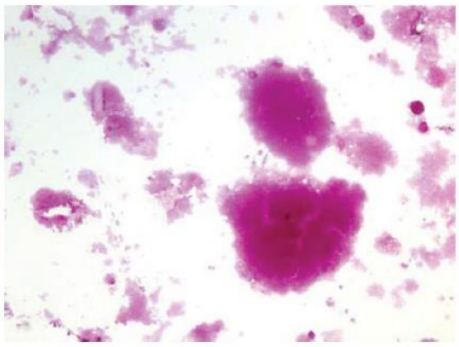

Figure 1. Positive PAS staining in BAL fluid cytology of PAP patients.[14]

Krebs Von De Lungen-6 (KL-6), a high molecular weight glycoprotein commonly used as a tumor marker and increased in lung cancer patients, especially adenocarcinoma, is also known as a marker of diffuse ILD. In a study using immunohistochemical examination of BAL fluid conducted found an increase in KL-6 values higher than KL-6 values in serum in PAP patients. This increase in KL-6 value in PAP patients is higher than the KL-6 value in other ILDs so that a sharp increase in KL-6 value indicates a diagnosis of PAP.[19] In addition to its role in PAP diagnostics, BAL is also useful as a management in PAP by performing whole lung lavage (WLL). The procedure is performed under general anesthesia using a double-bore endotracheal tube to ventilate one lung and perform lavage in the other lung. Rinses are performed using warm saline fluid totaling 5-40 L in one lung to remove lung surfactant.[13,20] Whole lung rinses in PAP are generally performed in stages in each lung with the more severely affected lung being performed first based on radiologic features. Subsequent lavage of the second lung is safer as the disease improves after the first whole-lung lavage therapy.[13] Repeated partial lung lavage can reduce KL-6 values in BAL fluid and serum followed by improvement in lung function and radiologic features.[19]

BAL measures can be used for follow-up PAP therapy.[21] PAP patients who received GM-CSF therapy, BAL fluid images before therapy showed fatty macrophages with extracellular protein material that gradually improved. After six weeks of GM-CSF therapy, extracellular amorphous material and cellular debris were no longer found. The macrophage population consisted of small monocyte-like cells without intracellular protein material (33%), large fatty macrophages with intracellular protein material (62%) and few large macrophages (3%). At the evaluation of 12 weeks of GM-CSF therapy, the macrophage population changed, consisting of macrophages containing fatty proteins (90%), only 10% of small monocyte-like macrophages and

no large macrophage cells. BAL fluid anti-GM-CSF antibody titers decreased from 4.4 $\mu$/mL before therapy to 0.14 $\mu$/mL after six weeks of therapy and 0.13 $\mu$/mL after 12 weeks of therapy.[22]

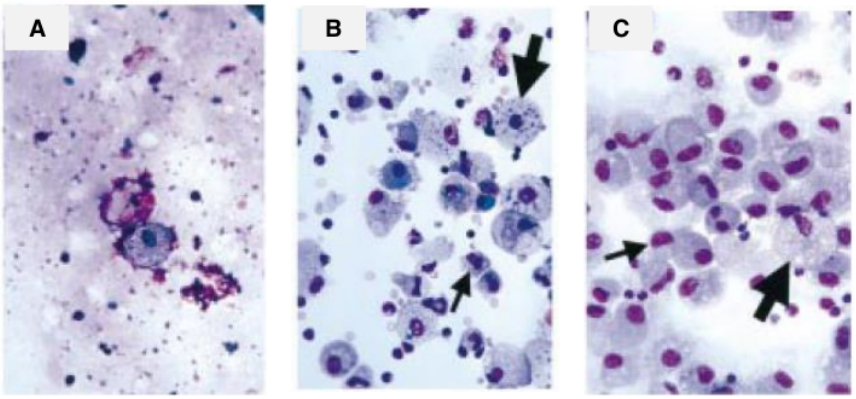


Figure 2. BAL fluid cytology before treatment (figure A), after six weeks treatment (figure B) and after 12 weeks treatment (figure C). Small arrows are small monocyte-like cells and large arrows are fat-containing macrophages.[22]

**Sarcoidosis**

Sarcoidosis is an idiopathic granulomatous systematic disease that affects the lungs and often involves multiple organs.[23] Symptoms often include shortness of breath, cough and fatigue. Spontaneous improvement occurs in many patients but some patients develop chronic disease. The etiology of sarcoidosis is still unknown, the presence of Th1 (T helper 1) CD4+ and macrophages in BAL fluid and blood is a factor in granuloma formation in the lung which is believed to be an autoimmune disease-causing antigen. The diagnosis of sarcoidosis is established by clinical and/or radiologic symptoms, as well as histologic findings of granulomatous non caseous inflammation by excluding other causes of local reactions. Granuloma formation is induced by antigen in the form of antigen-presenting cells (APC) to CD4+ naive T cells (Th0). Th0 cells will then be activated and differentiate into Th1 due to the influence of dendritic cells.[24] Suspicion of sarcoidosis is made if there is an increase in lymphocytes with negative mycobacterium culture from BAL fluid.[23]

At the time of diagnosis, 90% of patients with sarcoidosis have elevated lymphocytes in BAL fluid which is not affected by sarcoidosis staging. Patients with active sarcoidosis tend to have higher lymphocytes than those with inactive sarcoidosis although 10-15% of patients have normal lymphocyte counts. Neutrophil and mast cells are increased in advanced sarcoidosis. In addition, BAL also provides information through cell fraction analysis with T lymphocyte subset analysis.[25] T lymphocyte subset analysis (CD4/CD8 ratio) of elevated BAL fluid is an important finding in establishing the diagnosis of sarcoidosis. A CD4/CD8 ratio of more than 3.5 shows a high specificity of about 93-96% for sarcoidosis but has a low sensitivity of about 53-59%. Therefore, clinical support, typical radiological features of sarcoidosis and biopsy are required. However, assessment of CD4/CD8 ratio is still debatable due to the high variability of sarcoidosis.[25,26]

A prospective study was determined the cell pattern of BAL fluid in newly diagnosed sarcoidosis patients. This study divided patients into three groups, namely patients who were asymptomatic and did not receive corticosteroid therapy, patients who were symptomatic but not treated and symptomatic patients who had received corticosteroid therapy. The results showed that patients who did not receive therapy with sarcoidosis symptoms had an increase in lymphocytes and a higher CD4/CD8 ratio than asymptomatic patients. Symptomatic patients who had received corticosteroid therapy had lower lymphocytes and total BAL fluid cell counts than symptomatic patients who did not receive therapy.[28]

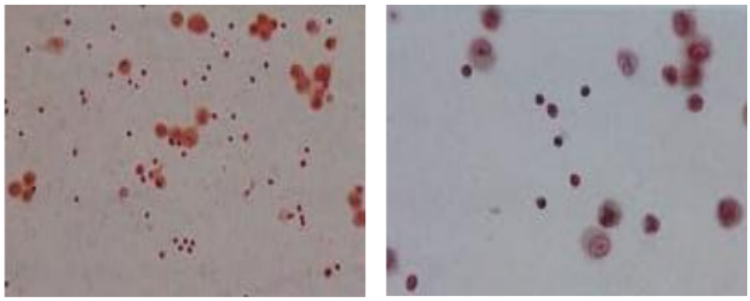

Figure 3. BAL fluid lymphocytosis in a sarcoidosis patient (using Papanicolaou's smear).[27]

Table 2. Characteristics of BAL fluid cell type counts of sarcoidosis patients and healthy individuals.[28]

| Cells | Healthy | Without symptom | With symptoms | Treated |
|---|---|---|---|---|
| Total cells (x$10^6$/mL) | 254±247 | 334±273 | 411±322 | 292±166 |
| Macrophages, % | 79±8 | 56,4±17 | 49,3±20 | 55,5±15 |
| Lymphocyte, % | 15,7±7 | 39±17 | 45±19 | 39±15 |
| Neutrophils, % | 5±2 | 4±4 | 5±5 | 5±3 |
| Eosinophils, % | 0,3±0,4 | 0,6±1 | 0,7±0,9 | 0,5±0,7 |
| CD4, % | 44±13 | 72±15 | 82±13 | 80±12 |
| CD8, % | 32±13 | 17±8 | 12±7 | 13±7 |
| CD4/CD8 | 1,7±1,0 | 5,7±4,5 | 9,3±5,0 | 8,3±4,8 |

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## CONCLUSION

Bronchoalveolar lavage is a minimally invasive procedure that is safe, easy to operate by operators and well tolerated by patients. Bronchoalveolar lavage is useful for the diagnosis and treatment of non-infectious lung diseases, such as pulmonary alveolar proteinosis and sarcoidosis.

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