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Role of Bronchoalveolar Lavage in Diagnosis

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1. Introduction

The lung is continuously exposed to the external environment and mixtures of complex antigens through the air. It is estimated that the resting human adult inhales 12,000 liters of air per day, while even mild physical activity can double or triple this amount (1). Protective immunity against inhaled antigens is mediated by the lymphocytes that are localized to the surface of the respiratory tract. The compartments in the lung where lymphocytes are present are (i) the epithelium and lamina propria of the air-conducting regions, (ii) the bronchus-associated lymphoid tissue (found commonly in certain animals i.e. rabbit and rats) (iii) the pulmonary interstitium and vascular beds (iv) the bronchoalveolar space. In addition to anatomical barriers, such as airway angulation, mucociliary clearance, and coughing, both humoral and cellular defense mechanisms play an important role in maintaining the viability of the host. One of the first lines of defense against particulate matter is mucociliary clearance and phagocytic activity of alveolar macrophages. Antigens entering the pulmonary tract encounter antigen-presenting cells comprised of alveolar and interstitial macrophages and effector T lymphocytes.

2. Bronchoalveolar lavage for diagnosis of various respiratory disorders

Bronchoscopy with bronchoalveolar lavage (BAL) is an important tool for the diagnosis of pulmonary infections and malignancies. Flexible fiberoptic bronchoscopy is a relatively safe and minimally invasive means by which to obtain bronchoalveolar lavage fluid (BALF). It is usually well tolerated by patients and can be performed safely even on those patients who are quite ill.

The diagnostic and prognostic utility of BAL was first evaluated in the 1980s (2). The investigatory technique of BAL has become one of the most valuable research tools for studying inflammatory mechanisms in a wide range of diseases that affect the lungs and airways in humans. In addition, cytological and microbiological testing of BAL samples are of established value for assisting in clinical diagnosis and management of many lung diseases, and these procedures are available routinely.

Since the introduction of the rigid bronchoscope by Dr. Jackson in 1904, BAL is a diagnostic procedure in which a fiber-optic bronchoscope is passed through the mouth or nose into the lung and fluid is put into a small part of the lung and then recollected for examination.

Bronchoalveolar lavage is typically performed to diagnose lung disease. Primarily, BAL was used as a treatment for patients who suffered from diseases associated with accumulation of purulent secretions such as alveolar proteinosis, cystic fibrosis and bacterial pneumonia (3).

3. Definition

By definition BAL is a method for the recovery of cellular and non-cellular components from the lower respiratory tract (e.g. alveoli) (4). It is a safe technique, with few major complications (5). In many cases (e.g. pulmonary proteinosis, alveolar hemorrhage, eosinophilic pneumonia) BAL can replace lung biopsy (6). Possible uses of BAL in diagnostics are summarized in following table

Non-infectious	Infectious
Sarcoidosis	(Ventilator-associated) pneumonia
Hypersensitivity pneumonitis	Pneumocystis pneumonia
Idiopathic lung fibrosis	Mycobacterial infection
Connective tissue disorders	Aspergillus fumigatus infection
Langerhans cell histiocytosis	Viral pneumonia
Malignancies	Toxoplasma pneumonia
Alveolar hemorrhage	Legionella infection
Alveolar proteinosis	Mycoplasma pneumoniae pneumonia
Eosinophilic pneumonia	Chlamydia pneumoniae pneumonia
Bronchiolitis obliterans with organizing pneumonia	Cryptococcal infection
Asbestosis	Histoplasma infection
Silicosis	Strongyloides infection

Table 1. Pulmonary diseases where BALF can be used to a diagnosis (7, 8, 9).

4. Procedure

Bronchoalveolar Lavage is a minimally invasive technique which is used to obtain cells, inhaled particles, infectious organisms and solutes from the alveolar spaces of the lung. To achieve this, a sufficient volume of lavage fluid must be instilled to ensure a sufficient aspirate. In adults, a minimum of 100 mL of lavage fluid should be instilled. Besides diagnostic BAL, there are other lavage techniques are used and they differ in the following ways: 1) Bronchial lavage (or bronchial washing) requires relatively little instilled fluid (10 - 30 mL) and samples from large airways for bacteriological study and/or tumour cytology; 2) therapeutic lavage uses small volumes and is used to remove sticky bronchial secretions in patients with asthma or cystic fibrosis; and 3) whole lung lavage is performed in order to

wash out an entire lung in patients with alveolar proteinosis, which requires repeated instillation of 1 L of fluid (in total 10–40 L for each lung) through a double-lumen endotracheal tube during general anaesthesia.

BAL is usually performed during fiberoptic bronchoscopy with topical anaesthetic after general inspection of the tracheobronchial tree. BAL can also be performed under general anaesthesia and in ventilated patients through a rigid bronchoscope or an endotracheal tube.

5. Site of bronchoalveolar lavage

The site of lavage depends on the localization of the abnormalities. In case of localized disease, for instance an infection with a radiographically apparent infiltrate or a malignancy, the involved segment should be sampled (10). In diffuse lung disease, the middle lobe or lingular lobe is commonly used as a standard site for BAL. This is often the most accessible site and the fluid obtained at one site is representative of the whole lung in diffuse lung diseases (11). If anatomical difficulties are encountered in both lobes the anterior segment of either the upper or lower lobe may be used. Using the method described, approximately 1.5–3% of the lung (approximately 1,000,000 alveoli) are sampled (4).

Usually, the lavage is performed using sterile, unbuffered isotonic saline (0.9% NaCl) solution and preferably the saline is preheated to body-temperature (37°C) to help prevent coughing and increase cellular yield (12). The volume varies between 100 and 300 ml in aliquots of 20 to 50 ml (13). The ERS task force recommended the use of 200–240 ml divided in four aliquots.

5.1 Fluid instillation and recovery

The fluid is instilled with syringes through the biopsy channel of bronchoscope and immediately recovered by applying suction (25–100 mmHg), using a standard number of input aliquots of 20–60 mL (commonly four to five aliquots are recommended) up to a total volume of 100–300 mL. Smaller instilled volumes (<100 mL) increase the likelihood of contamination by the bronchial spaces, including inflammatory cells derived from the larger airways, which may skew the differential cell counts [14].

The first aspirated volume is normally smaller than the following ones. Usually, 40–70% of the instilled volume is recovered. In obstructive airway disease and emphysema the recovery rate is significantly lower and may be <30%. The yield is also reduced in healthy smokers and the elderly. In addition, fluid recovery may be low with a poor wedge position leading to leakage of lavage fluid around the bronchoscope, which is associated with cough. Differential evaluation of the “bronchial” (first aliquot) and “alveolar” (subsequent aliquots) samples may be useful in airway diseases. Siliconised or plastic containers should be used for collection and processing of BAL fluid to avoid loss of cells through adhesion to glass surfaces.

6. Safety aspects

The BAL procedure is practically associated with no mortality and carries a low complication rate of 0–2.3% [15–17]. After BAL procedure there is fever in some hours and a

transient decrease in lung function parameters, both usually self-limited and resolving within 24 h. These are the most frequent adverse effects and occur in 3–30% of patients, depending on the instilled volume. Other adverse effects include short-lasting alveolar infiltration, wheezing and bronchospasm in patients with hyper-reactive airways. Major or late complications are only seen in patients with severe lung or heart disease, and bleeding has only been reported in patients with clotting disorders or thrombocytopenia. Risk factors for developing adverse effects are: 1) extensive pulmonary infiltrates, an arterial oxygen tension <8.0 kPa (<60 mmHg) and an oxygen saturation $<90\%$; 2) a forced expiratory volume in 1 s <1.0 L; 3) prothrombin time >50 s and platelet counts $<20,000$ platelets/mL; 4) significant comorbidity; and 5) bronchial hyperreactivity.

6.1 Quality control of BALF

To ensure that the obtained material represents the situation in the alveoli, a number of criteria have been established. A BALF is regarded non-representative if it fulfills one of the following criteria: i) volume <20 mL, ii) total cell count $<60,000$ cells/mL, iii) presence of $>1\%$ squamous epithelial cells, iv) presence of $>5\%$ bronchial epithelial cells, v) presence of extensive amounts of debris, vi) severely damaged cell morphology.

6.2 Specimen processing

The total fluid recovered is kept at room temperature and should be transported to the laboratory within 1 hr because the cells are not well preserved in the saline solution. The fluid should be pooled into a single container and total volume should be measured. The lavage fluid frequently contains large amounts of mucus; therefore, filtration through cotton gauze or nylon mesh is often performed. Filtration leads to a preferential loss of bronchial epithelial cells without a significant effect on the total cell count and cell differentials. After filtration, the fluid is centrifuged for 10 min at 500g and after this the supernatant can be stored at -20°C or -70°C for subsequent analysis of soluble components. The total number of cells is counted in a haemocytometer, either in a sample of the pooled native fluid or in a resuspension of the cells after the first centrifugation. Washing procedures result in a loss of total cell count but lead to an increase in cell viability of the remaining cells. The total cell count is usually expressed as the total number of cells recovered per lavage but also as the concentration of cells per mL of recovered fluid. Cell viability is assessed by trypan blue exclusion and should range from 80% to 95% [18, 19].

For the enumeration of cell differentials, at least 600 cells are counted on cytocentrifuge or cell smear preparations after staining with May-Grunwald-Giemsa stain. A high percentage of epithelial cells ($>5\%$) is indicative of contamination of the alveolar samples by bronchial cells. At least three unstained slides should be stored so that special stains (iron, periodic acid-Schiff (PAS), silver, toluidine blue, fat or Ziehl-Neelsen) can be performed as per need.

Besides these routine investigations, further work-up can be performed as needed. For example, if a tumor is suspected the Papanicolaou stain can be applied. If infection is suspected, a complete microbiological assessment, including cultures, should be performed. To document asbestos exposure, quantitative determination of asbestos bodies can be made after vacuum filtration of the native BAL fluid through a $0.45\text{--}1.2\text{ }\mu\text{m}$ Millipore membrane. The exact dust composition can be determined by electron microscopy with energy

dispersive X-ray spectrometry. Lymphocyte subpopulations can be identified by immunocytochemical methods, immunofluorescence or flow cytometry using monoclonal antibody techniques [20].

These investigations are not recommended as a routine procedure for all BAL specimens. They are indicated in cases with high lymphocyte counts, such as extrinsic allergic alveolitis, or if Langerhans cell histiocytosis is suspected. CD3, CD4, CD8, CD20 and markers of T-cell activation can be determined. CD1a or Langerin are very specific markers of Langerhans cell histiocytosis. Flow cytometry is also a useful tool to detect markers of malignant lymphoma [21].

There are some studies also performed for research purposes including functional studies of viable BAL cells, cell cultivation in appropriate culture medium and determination of mediators along with the mechanisms that appear to regulate the mediator release. Cells can also be probed with molecular biology to investigate gene activation and intracellular signaling pathways.

7. Normal values of BAL in healthy volunteers

The BAL fluid obtained from healthy, nonsmoking adults without lung disease contains only small percentages of lymphocytes, neutrophils and other inflammatory cells; alveolar macrophages are the predominant cell population (80–90%) (fig. 1a). Differential cell count in healthy non-smokers have been reported to show macrophages >80%, lymphocytes ≤15%, neutrophils ≤3%, eosinophils ≤0.5%, and mast cells ≤0.5%.

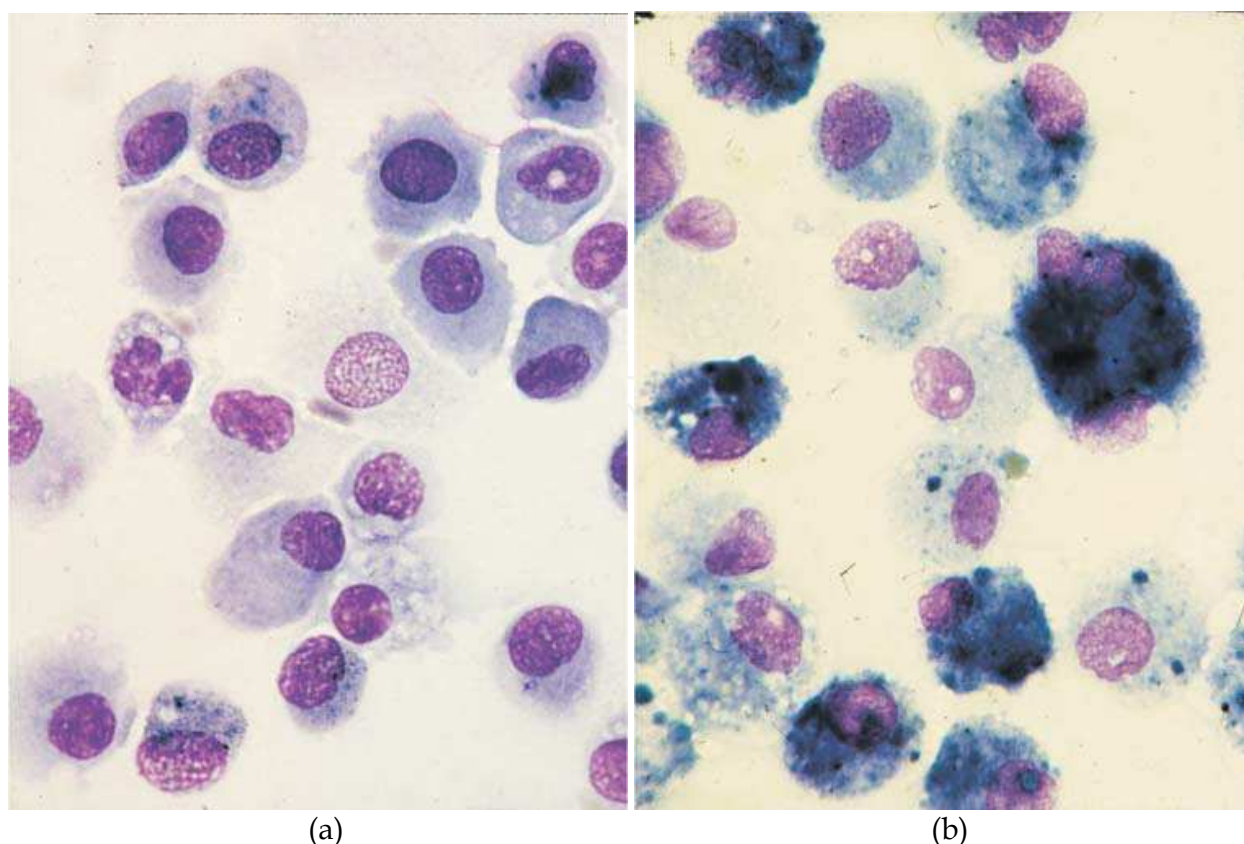


Fig. 1. Bronchoalveolar lavage in a) a healthy nonsmoker and b) a healthy smoker [22].

Cigarette smoking is a strong confounding factor with significant effects on BAL samples. The alveolar macrophages from smokers show a 3 to 5 fold increase and characteristic morphology: many of them are much larger than those in nonsmokers and contain cytoplasmic inclusion bodies (smoker's inclusion bodies) consisting of tar products, lipids, lipofuscin and other substances (fig. 1b).

7.1 BAL in the diagnosis of diffuse parenchymal lung disease

BAL is indicated in every patient with nuclear pulmonary shadowing or interstitial lung disease (ILD). BAL findings may be very specific, so that they can directly confirm a particular diagnosis. BAL should not be considered as a stand-alone diagnostic test and should be interpreted in the context of clinical, laboratory and radiographical high resolution computed tomography (HRCT) findings. It has been used in diagnostic and prognostic evaluation in diffuse parenchymal lung disease for three decades and has a central role in the diagnosis of a number of rare disorders and in excluding opportunistic infection in treated patients. It also has an important role in the diagnosis of many prevalent disorders, including sarcoidosis, hypersensitivity pneumonitis and idiopathic pulmonary fibrosis.

7.2 Specific BAL findings in rare diseases

7.2.1 Pulmonary alveolar proteinosis

Pulmonary alveolar proteinosis is one of the few diseases in which BAL can confirm the diagnosis and replace lung biopsy. In pulmonary alveolar proteinosis the BAL fluid is macroscopically milky and turbid. Under light microscopy the characteristic acellular oval bodies (surfactant derived lipoproteins) are basophilic on May-Grunwald-Giemsa staining and positive with PAS staining. The background is occupied by large amounts of amorphous debris showing weak PAS staining and a few foamy macrophages [21].

7.2.2 Langerhans cell histiocytosis

Pulmonary Langerhans cell histiocytosis is strongly associated with cigarette smoking, and the BAL differential shows the typical smoker's constellation with increased total cell counts and macrophages with smoker's inclusions. The specific finding is an increase in Langerhans cells to >4% of the total BAL cell count. The sensitivity is low because in late cases of the disease the number of Langerhans cells decrease in the tissue. Low proportions of Langerhans cells in the range of 2-4% can be seen in other conditions, such as in healthy smokers, respiratory bronchiolitis/interstitial lung disease (RB/ILD), other ILD and bronchioalveolar carcinoma [21]. The Langerhans cells can be easily identified in BAL by their staining with the monoclonal antibody for CD1a or Langerin [23]. The intracytoplasmic reaction with polyclonal antibody S100 is not as specific. As in alveolar proteinosis, electronic microscopy is not recommended as a routine diagnostic procedure.

7.2.3 Diffuse alveolar haemorrhage

Diffuse alveolar haemorrhage (DAH) is a clinical syndrome with widespread bleeding into the alveolar space as a result of multiple causes. The demonstration of numerous

haemosiderin-laden macrophages on BAL cytology enables a diagnosis to be made even in cases with occult bleeding. In patients with fresh bleeding episodes free red blood cells in the fluid and fragments of ingested red blood cells within the cytoplasm of macrophages are pathognomonic.

To assess the severity of bleeding, the percentage of siderophages can easily be counted. It has been shown that a percentage of siderophages $\geq 20\%$ is sufficient for a diagnosis of DAH.

Many syndromes belong to this group and other clinical and laboratory findings must be investigated to establish the cause of the bleeding. In the clinical setting, chronic left heart failure with pulmonary congestion is one of the most frequent underlying conditions for the finding of DAH in BAL fluid examination. Endogenous bleeding has to be differentiated from exogenous iron load of the lungs. Exogenous siderosis does not show roundish fragments of erythrocytes but irregular shaped dust particles engulfed by macrophages.

7.2.4 Chronic aspiration

In the differential diagnosis of recurrent pneumonia, gastro-oesophageal reflux with aspiration needs to be considered. The BAL cell differential may show a mixed pattern with increase in lymphocytes, neutrophils and eosinophils. The characteristic diagnostic finding is the presence of large numbers of lipid-laden macrophages and is highly suggestive of lipoid pneumonia caused by chronic aspiration.

7.2.5 Pneumoconioses

In ILD due to mineral dust exposure, BAL can confirm exposure by the detection of dust particles in alveolar macrophages. It is of two types:

- a. Asbestos-related disease: Asbestos bodies in BAL fluid can be detected by smear technique or cytocentrifuge technique. However quantification of asbestos bodies by a specific Millipore filtration is a more sensitive technique. The results are expressed as number of asbestos bodies per mL of BAL fluid, which shows a relatively good correlation with the asbestos body count in lung tissue analysis. However, 10–15% of subjects with known occupational asbestos exposure may have no detectable asbestos bodies in their BAL fluid. Thus, a negative BAL asbestos body count does not exclude asbestos-related disease.
- b. Chronic beryllium disease: This condition is clinically, radiologically and histologically identical to sarcoidosis and in this condition BAL lymphocytes have an increase in the CD4/CD8 ratio. Because the antigen is known, a diagnostic in vitro lymphocyte transformation test can be performed. Lymphocytes from blood or BAL fluid are incubated with beryllium salts and the beryllium-specific proliferation of the lymphocytes is quantified. A positive lymphocyte transformation test of BAL T-cells to beryllium salts is highly sensitive and specific (definitely more sensitive than the blood test) and always recommended in doubtful cases to confirm the diagnosis.

7.2.6 Eosinophilic lung disease

Eosinophilic lung disease can be diagnosed when there are $\geq 25\%$ eosinophils in BAL of the radiologically affected segment. In both acute and chronic eosinophilic pneumonia the

fraction of BAL eosinophils ranges from 20% to 90% and is higher than the neutrophil fraction. In this condition a mild-to-moderate increase in lymphocyte count with a decrease in CD4/CD8 ratio can be observed. In combination with clinical and HRCT findings, eosinophilic lung diseases can be appropriately diagnosed by BAL alone without an open lung biopsy [21].

7.2.7 Opportunistic infections

BAL has achieved the greatest diagnostic value among immunocompromised patients with pulmonary infiltrates. The sensitivity of BAL ranges from 60–90% in the diagnosis of bacterial infections, 70–80% in mycobacterial, fungal and most viral infections, and from 90–95% in *Pneumocystis carinii* pneumonia. The characteristic cysts of *Pneumocystis* can be detected on May-Grunwald-Giemsa stained slides.

In cytomegalovirus pneumonia, the characteristic cytomegalic-transformed cell (the owl eye cell) with typical nuclear or cytoplasmic inclusions is highly specific and can be seen on light microscopy in 30–50% of cases.

7.2.8 Malignancies

BAL is not as sensitive for solid tumours as biopsy and cytology techniques. Diffuse malignant infiltrates can be reliably diagnosed in 60–90% of cases. The highest yield is seen in widespread malignancies, such as primary bronchoalveolar carcinoma or lymphangitic carcinomatosis due to adenocarcinoma. It can also provide diagnostic cytological material in haematological malignancies of the lung, including Hodgkin's disease, non-Hodgkin lymphoma, leukaemia, Waldenstrom's macroglobulinaemia, myeloma and mycosis fungoides. In malignant B-cell lymphoma the immunocytological demonstration of a monoclonal B-cell population, expressing only one immunoglobulin type and either kappa or lambda light chains, can confirm the diagnosis of malignancy [24, 25].

8. BAL as an adjunct to diagnosis

There are no specific BAL findings in the more common interstitial lung diseases. However, when BAL cellular analysis is considered in the context of clinical and HRCT findings it may contribute to narrowing the differential diagnosis and to avoiding open lung biopsy. BAL cellular patterns can generally differentiate the fibrosing conditions (characterised by neutrophilia and eosinophilia) from granulomatous diseases (lymphocytosis with or without granulocytosis).

8.1 Sarcoidosis

In sarcoidosis, BAL shows lymphocytic alveolitis in 90% of patients at the time of diagnosis, independent of the stage of sarcoidosis. It was shown that the patients with active sarcoidosis have a tendency to show higher lymphocyte counts than those with inactive sarcoidosis. However, in the late stage of sarcoidosis neutrophils may also be increased, as well as the number of mast cells. Patients with primary extrathoracic sarcoidosis may show typical findings of sarcoidosis on BAL even when imaging findings are normal [26]. The CD4/CD8 ratio also has high variability in sarcoidosis and approximately only 55% of

patients show an increased CD4/CD8 ratio at the time of diagnosis. The ratio is even decreased to 1.0 in 15% of patients. The CD4/CD8 ratio is especially high in patients with Lofgren syndrome and acute sarcoidosis. Some studies have demonstrated an increased neutrophil count in BAL obtained from newly diagnosed patients with sarcoidosis.

8.2 Extrinsic allergic alveolitis

This disease shows the highest total cell count and the highest lymphocyte count of all ILDs. The total cell yield is usually >20 million from a 100-mL BAL, with the proportion of lymphocytes exceeding 50%. The number of activated T-cells is also increased. The assessment of the CD4/CD8 ratio has produced contradictory findings. It is a general belief that the CD4/CD8 ratio is decreased. However, more recent studies have demonstrated that the ratio may be decreased, normal or increased [27, 28]. The alveolar macrophages are heterogeneous and often show a foamy cytoplasm. In acute episodes of extrinsic allergic alveolitis, the neutrophil count may increase transiently for approximately one week. A normal cell appearance or an isolated increase in neutrophil or eosinophil count widely excludes extrinsic allergic alveolitis.

8.3 Drug induced pneumonitis

There are a large number of drugs which may induce an ILD, mediated by either toxic or immunological mechanisms (Table 2) [29]. Along with BAL lymphocytosis and/or granulocytosis, cytotoxic reactions with atypical type II pneumocytes or diffuse alveolar haemorrhage may be observed. The most frequent finding is lymphocytic alveolitis with a dominance of CD8+ T-cells. Methotrexate-induced pneumonitis may show an increase in CD4+ cells. Characteristic changes in amiodarone-induced pneumonitis are the presence of alveolar macrophages with a finely vacuolated foamy cytoplasm. These are also seen in patients without clinical signs of ILD. If no foamy macrophages are found, amiodarone-induced pneumonitis can probably be excluded. The BAL findings described are not specific for drug-induced lung disease; therefore, additional assessment including tests like anti-histone antibody is necessary to make the diagnosis.

8.4 Idiopathic pulmonary fibrosis and other idiopathic interstitial pneumonias

The typical BAL findings in idiopathic pulmonary fibrosis (IPF) is a moderately increased neutrophil count (10-30% of the total cells), with or without an increased eosinophil count. In total, 70-90% of the patients show an increased neutrophil count, while 40-60% shows an additionally increased eosinophil count. In 10-20% of the patients, a moderately increased lymphocyte count (proportion <30%) is seen.

In nonspecific interstitial pneumonia (NSIP), a BAL lymphocytosis with a mild increase in the neutrophil and eosinophil count can be seen [30]. A BAL lymphocytosis is likely to be found more frequently in cellular NSIP than in fibrotic NSIP. The BAL findings in cellular NSIP appear to resemble those in bronchiolitis obliterans organizing pneumonia (BOOP).

In acute interstitial pneumonia the histological finding of diffuse alveolar damage shows an extremely unfavourable prognosis. The BAL fluid in acute interstitial pneumonia is mostly bloody and rich in albumin, indicating increased alveolar capillary permeability. The typical

Lymphocytosis	Eosinophilia	Neutrophilia	Cytotoxic reaction	Haemorrhage
Methotrexate	Bleomycin	Bleomycin	Bleomycin	D-Penicillamine
Azathioprine	Nitrofurantoin	Minocycline	Methotrexate	Amphotericin B
Cyclophosphamide	Cotrimazole	Amiodarone	Nitrosoureas	Cytotoxic drugs
Bleomycin	Penicillin		Busulfan	
Busulfan	Sulfasalazine		Cyclophosphamide	
Vincristine	Ampicillin			
Nitrofurantoin	Tetracycline			
Minocycline	Maloprim			
Gold	Minocycline			
Sulfasalazine	L-Tryptophan			
Amiodarone				
Acebutolol				
Atenolol				
Celiprolol				
Propranolol				
Flecainide				
Diphenylhydantoin				
Nilutamide				

Table 2. Bronchoalveolar lavage findings in drug-induced interstitial lung disease

cellular BAL finding is a marked increase in neutrophils and an occasional increase in lymphocytes. Atypical pneumocytes mimicking adenocarcinoma and fragmented hyaline membranes may also be observed [25]. The typical BAL findings in desquamative interstitial pneumonia and RB/ILD are an increase in macrophages with black pigmented inclusions. In this an increase in neutrophils, eosinophils and, occasionally, lymphocytes may also be seen. Idiopathic lymphocytic interstitial pneumonia is rare and is usually associated with collagen vascular diseases, Sjogren’s syndrome or lymphoma. The typical BAL finding in lymphocytic interstitial pneumonia is lymphocytosis and CD4/CD8 ratio shows diverse alterations.

8.5 Collagen vascular disease

In collagen vascular diseases (CVD), pulmonary involvement can be associated with various histopathological patterns. The pathology may be similar to IPF with a usual

interstitial pneumonia pattern, but many of the cases of CVD-associated pulmonary fibrosis show a pattern that is in the category of NSIP, based on a computed tomography scan or histology [26]. The BAL findings are also somewhat different from IPF. The general pattern is increased neutrophils, with or without eosinophils, but increased lymphocytes are more commonly seen than in IPF [31]. In general, BAL seems to have a limited value in the diagnosis of CVD affecting the lungs because the BAL profile is very nonspecific. However, BAL may be useful in detecting other pulmonary problems that may arise in these disorders, including drug induced toxicity, infection, pulmonary haemorrhage associated with vasculitis and malignancy. The NSIP pattern was the more prevalent pattern. It has previously been shown that increased BAL neutrophils were associated with more extensive changes on HRCT. An abnormal BAL may be the first evidence of pulmonary involvement in CVD. If radiographic signs are absent and pulmonary function tests are normal, this abnormal finding indicates subclinical alveolitis. It is still not clear whether such subclinical alveolitis needs treatment. It is also not clear whether the pattern of BAL cells (increase in neutrophils or lymphocytes) in a setting of subclinical alveolitis reflects the prognosis [32].

9. Role of BAL in the prognosis and activity of disease

It is unclear whether BAL cellularity is useful for assessing the activity of disease processes with respect to obtaining prognostic information. In sarcoidosis, differences were observed for several BAL parameters between clinically active and inactive patient groups, but without predicting long-term outcome in individual patients. It is not proven that BAL or serial BAL is useful to guide therapy or predict treatment response. At present, BAL cannot be routinely recommended for this purpose.

10. Role of BAL in research and development of new drugs

The discovery of new signal pathways and biomarkers between cells and the application of proteomics, gene arrays and metabolomics has contributed many important insights into the pathogenesis of respiratory tract diseases. BAL has been profiled as a fundamental method to obtaining alveolar space and airway specimens for research, and this could lead to more clear-cut longitudinal monitoring of ILD in the future. For example, KL-6, a high-molecular weight glycoprotein predominantly expressed on the surface of alveolar type II cells, is a promising biomarker in the field of ILD. Increased levels of KL-6 in BAL fluid and plasma correlate with the severity of alveolar inflammation and poor survival in acute respiratory distress syndrome [33]. Increased levels of KL-6 in both BAL fluid and blood, with a strong correlation between BAL and blood, also reflect disease severity in patients with idiopathic pulmonary alveolar proteinosis [34]. BAL is suitable for studying the cellular and biological changes induced by drugs. In this view, BAL can be used for concept studies in the clinical development of new drugs.

11. Conclusion

Bronchoalveolar lavage is an easily performed and well tolerated procedure able to provide cellular contents, cellular products, and proteins from the lower respiratory tract.

In the rapidly evolving field of pulmonary diagnostic tests, BAL has a specific value for the diagnosis of certain ILD's, such as alveolar proteinosis, Pneumocystis pneumonia, bronchoalveolar carcinoma, malignant non-Hodgkin lymphoma and alveolar haemorrhage, allowing surgical lung biopsy to be avoided. In other ILD's, BAL findings may be able, in combination with clinical and HRCT findings, to strengthen or weaken a suspected diagnosis. This method is also valid support for research. Genetic and molecular biomarkers, with different diagnostic/prognostic significance, can be detected in BAL.

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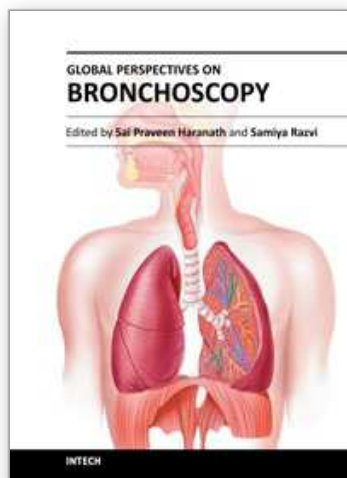
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Bronchoscopy has become an essential part of modern medicine . Recent advances in technology have allowed integration of ultrasound with this tool. The use of lasers along with bronchoscopes has increased the therapeutic utility of this device. Globally an increasing number of pulmonary specialists, anaesthesiologists and thoracic surgeons are using the bronchoscope to expedite diagnosis and treatment. The current volume on bronchoscopy adds to the vast body of knowledge on this topic. The democratic online access to this body of knowledge will greatly increase the ease with which both trainees and expert bronchoscopists can learn more .The contributions from around the world cover the breadth of this field and includes cutting edge uses as well as a section on pediatric bronchoscopy . The book has been an effort by excellent authors and editors and will surely be a often reviewed addition to your digital bookshelf. . In summary, this book is a great testament to the power of collaboration and is a superb resource for doctors in training, ancillary team members as well as practicing healthcare providers who have to perform or arrange for bronchoscopy or the associated procedures.

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