Curr Pulmonol Rep (2015) 4:117–124
DOI 10.1007/s13665-015-0122-8

INTERSTITIAL LUNG DISEASE (E ALHAMED, SECTION EDITOR)

Role of broncho: alveolar lavage in approaching interstitial lung diseases

Mohammad Khan[1] · **Nahid Sherbini**[1] · **Hamdan AL-Jahdali**[1]

Published online: 30 July 2015

Abstract Bronchoalveolar lavage (BAL) is a simple and safe procedure performed during flexible bronchoscopy. BAL provides an important diagnostic tool in the diagnosis of various diffuse lung diseases. BAL fluid analysis for cell count and differential, bacteriology and cytology may suggest specific disease or give alternative diagnosis. Nevertheless, BAL is seldom useful as a "stand-alone" diagnostic test for various diffuse pulmonary diseases. Confident diagnoses can be obtained when clinical evaluation and high-resolution computed tomography of the chest (HRCT) findings are combined with BAL fluid analysis and/or transbronchial lung biopsy. BAL may also be helpful in determining the response to treatment and prognosis of interstitial pulmonary disease. This review is about the role of BAL in approaching patients with interstitial lung diseases (ILDs) and will describe the value of different cell patterns found.

Keywords Bronchoalveolar lavage (BAL) · Interstitial pulmonary fibrosis (ILD) · Idiopathic pulmonary fibrosis (IPF) · Bronchoscopy

This article is part of the Topical Collection on *Interstitial Lung Disease*

✉ Hamdan AL-Jahdali
Jahdali@yahoo.com

[1] Department of Medicine, Pulmonary Division, King Abdulaziz Medical City, King Saud University for Health Sciences, PO Box 101830, 11665 Riyadh, Saudi Arabia

Introduction

Bronchoalveolar lavage (BAL) is a simple and safe procedure performed during flexible bronchoscopy to collect aspirated fluids containing alveolar cells. Analysis of BAL cell counts, differentials, cultures and cytology provides valuable data for diagnosis and management of many respiratory diseases [1].

Interstitial lung diseases (ILDs) or diffuse parenchymal lung disease (DPLD) represent an expansive conglomerate of acute and chronic disorders that are classified on the basis of similar radiographic, clinical or pathologic manifestations. BAL findings of different nucleated inflammatory cell patterns often had characteristics that are highly consistent with various forms of ILD, such as idiopathic pulmonary fibrosis (IPF), hypersensitivity pneumonitis (HP) or sarcoidosis.

The main classifications of ILDs are those with known and unknown causes. The known causes are drugs, ILDs associated with connective tissue disease, HP and sarcoidosis. The other group are those with unknown causes called idiopathic interstitial pneumonia (IPF) which are further classified to IPF and idiopathic interstitial pneumonias (IIP) other than IPF including non-specific interstitial pneumonia (NSIP), lymphoid interstitial pneumonia (LIP), desquamative interstitial pneumonia (DIP), respiratory bronchiolitis related interstitial lung diseases (RB-ILD), and cryptogenic organizing pneumonia (COP). Although these diseases largely share common clinical features, a precise diagnosis is mandated as treatment and prognosis vary with distinct histological features [2, 3••].

Diagnostic algorithm for all sub-groups of ILDs requires an evaluation including a full medical history (with occupational, hobbies, and environmental exposures or drug history), family history, and physical examination, lung function tests, chest radiographs and laboratory investigations including auto antibodies. If these initial diagnostic tests did not show the

diagnosis, more interventions would be needed such as bronchoscope with BAL for cellular analyses and transbronchial lung biopsy. Surgical lung biopsy may be indicated if previous investigations were inconclusive.

Differential cell count of BAL is very useful for differential diagnosis of numerous sub-groups of ILDs [4]. Confident diagnoses can be obtained when clinical evaluation and high-resolution computed tomography of the chest (HRCT) findings are combined with BAL fluid analysis and/or transbronchial lung biopsy. Characteristic features of HRCT or BAL may preclude the demand for surgical lung biopsy for many sub-groups of ILDs, such as IPF or sarcoidosis [5].

This chapter will review the role of BAL in approaching patients with ILDs and will describe the value of different cell patterns found.

Bronchoscopy: BAL and transbronchial biopsy

Bronchoscopy with BAL is a routine procedure performed frequently by pulmonologists. It is considered a minimally invasive and generally well-tolerated procedure with very low overall morbidity and mortality [6, 7]. The analysis of BAL according to good clinical laboratory practice by qualified personnel with an experience in BAL cytological analysis about the findings of different sub-groups of ILDs is very important.

Many different BAL protocols have been produced and commonly consist of multiple aliquots (the retrieved liquid from BAL) that usually require from five or six aliquots of 20 mL each to four aliquots of 60 mL each. The right middle lobe and lingula are the more accessible regions of the lung with a high likelihood to allow a good return of BAL [8••, 9]. BAL fluid of a healthy, never-smoker patient should contain, approximately, 80–90 % alveolar macrophages, 5–15 % lymphocytes, and 3 % neutrophils and/ or 1 % eosinophils. The presence of squamous epithelial cells indicate that the BAL fluid has been polluted by oropharyngeal secretions, which may suggest the use of poor technique in performing the BAL [10]. HRCT findings demonstrate the involved segments which should be used as a guide to the best areas of sampling by BAL. Evidence suggests that this diagnostic procedure might be more useful if it was targeted to one of the pulmonary segments most affected, as identified by chest HRCT [5]. Routine sampling of BAL fluid with cellular analyses for patients with ILD includes total and differential cell counts as well as the morphological appearances of cells, besides cultures and special stains for infection is recommended [1].

Other confounding factors, such as smoking history, age and medications that might influence the inflammatory cells into the lung (e.g. corticosteroids and other immunomodulating agents), need to be considered in interpreting the cellular pattern of the BAL. Another important confounder is infection that can stimulate the sub-acute onset of diffuse lung infiltrates or coincide with non-infectious ILD. As a result, BAL should be inspected and screened for mycobacterium or fungal infection should infectious aetiology be clinically suspected [11].

BAL findings in ILDs according to cellular components

Normal BAL components contain a majority of alveolar macrophages (80–90 %), lymphocytes (5–15 %), and neutrophils (3 %) or eosinophils (1 %) [10]. There are a wide variety of cells that may be present in BAL fluid of patients with ILDs, which may suggest specific diagnosis (Table 1). Depending on the cause, the predominant cell type found will help in the approach for confident diagnosis in ILD [12, 13••]. One study revealed that BAL cell count is very useful for diagnosis of common ILD disease such as HP and sarcoidosis but has less diagnostic yield for rare forms of ILDS disease [14]. An additional evidence of 237 BAL samples from patients with ILD such as cryptogenic organizing pneumonia, idiopathic pulmonary fibrosis, hypersensitivity pneumonitis, sarcoidosis and smoking-related ILD found compelling disparities in the BAL cell counts of healthy controls and patients with ILDs sub-groups examined in this study [15].

Lymphocytic cellular pattern in BAL

A lymphocytic BAL pattern is commonly seen in granulomatous lung diseases, such as HP, sarcoidosis and some drug reaction cases [16]. An increased lymphocyte count driven predominantly by activated T helper cells with a high CD4:CD8 ratio is a typical finding of pulmonary sarcoidosis and considered adequate for the diagnosis of sarcoidosis. However, both the frequency of lymphocytes in BAL and the BAL CD4:CD8 ratio can be variable [17]. On the other hand, in HP, not only increasing the number of lymphocytes but also increasing the absolute neutrophil and eosinophill counts may be significantly increased [18]. Increased number of CD4-positive BAL lymphocytes may also be seen in methotrexate pneumonitis and chronic beryllium disease [19]. Unfortunately, a lymphocytic BAL does not distinguish between farmers with HP and exposed asymptomatic farmers who may remain asymptomatic and not progress to a clinically relevant disease, despite their elevated BAL lymphocyte count [20]. BAL lymphocytosis appears also to be common in the cellular type of NSIP [21]. Finally, lymphocytic predominant pattern in BAL has been expressed in Wegener's granulomatosis, primary biliary cirrhosis and Crohn's disease [22].

Neutrophilic cellular pattern in BAL

Elevated neutrophils in BAL are commonly found in idiopathic pulmonary fibrosis (IPF), aspiration pneumonia, sub-acute

Table 1 BAL findings in ILDs

ILD	BAL findings	Common radiological findings
Normal BAL	Alveolar macrophages (80–90 %), Lymphocytes (5–15 %), Neutrophils (3 %) Eosinophils (1 %)	Normal
IPF	Mild to moderate lymphocytic pattern with higher neutrophils.	Bilateral interstitial reticular, fibrotic basal sub-pleural infiltrate with or without honeycombing.
NSIP	BAL lymphocytosis of >30% with mildly elevated neutrophils.	Bilateral diffuse ground –glass opacities with more basal, sparing the sub-pleural areas.
LIP	Same as NSIP	Bilateral diffuse ground –glass opacities.
DIP/RB-ILD	Same as NSIP	Bilateral diffuse ground –glass opacities.
Sarcoidosis	Marked Lymphocytic pattern with predominant high CD4/CD8 T cell ratio.	Bilateral hilar adenopathy with or without bilateral diffuse interstitial infiltrates, pulmonary nodules and fibrosis also may found.
HP- Hypersensitivity pneumonitis	Marked lymphocytosis and the CD4/CD8 ratio are low. Mast cells Plasma cells and Foamy macrophages may also present.	History of exposure to known antigen combined with typical ground-glass centro-lobular nodules mainly in upper lung lobes, also diffuse and fibrotic changes may be described.
Drug-induced ILDs	Mixed inflammation with moderate lymphocytic and mild Neutrophilic pattern.	Patchy or diffuse infiltrates plus drug history to use a pneumotoxic and cause interstitial changes.
COP	Lymphocytic pattern and mild eosinophils with low CD4/CD8 ratio.	Bilateral patchy alveolar infiltrates (fleeting airspace disease).
CTD related ILDs	Neutrophils and lymphocytes are predominant.	Variable bilateral alveolar or interstitial infiltrates.
Systemic sclerosis-ILDs (scleroderma-ILDs)	Presence of increased numbers of neutrophils, eosinophils and alveolar macrophages with low CD4/CD8 ratio.	Variable bilateral alveolar or interstitial infiltrates with or without picture of UIP pattern.
Pneumoconiosis -occupational exposures	Dust or coal particles may found but BAL mainly to rule out infections and malignancies. Normal or High CD4/CD8 ratio	Variable bilateral alveolar or interstitial infiltrates.
PLCH	CD1a+cells 0.4 %	Bilateral diffuse cystic changes with pulmonary nodules.
Lymphangioleiomyomatosis-LAM	To rule out infections and malignancies.	Bilateral diffuse cystic changes
Alveolar proteinosis	Milky fluid, periodic acid–Schiff-PAS, positive a cellular corpuscles and foamy macrophages.	Bilateral diffuse infiltrates with a crazy-paving description.
DAH	Bloody sequential retrieve, RBCs and later "Hemosiderin-laden macrophages".	Bilateral central alveolar infiltrates.
Lipoid pneumonia	Foamy or "lipid-laden" macrophages	Bilateral patchy alveolar infiltrates mostly in the dependent areas.

HP, bronchiolitis obliterans (BO) and in many pulmonary infections [22, 23]. Increased neutrophil count with or without mild eosinophilia is reported in the BAL of 70–90 % of patients with IPF but is not specific [23].

Eosinophilic cellular pattern in BAL

A considerable increase in the BAL eosinophil count (≥25 %) is a typical finding of tropical pulmonary eosinophilia, acute eosinophilic pneumonia or chronic eosinophilic pneumonia (CEP) [24]. Modest increases in BAL eosinophils (<25 %) may be observed in pulmonary Langerhans cell histiocytosis, IPF, connective tissue diseases, drug-induced pneumonitis and sarcoidosis [25]. One study showed that the eosinophilic pneumonia particularly presented with a significant increase in eosinophil counts and a cogent decrease in T cell proportions, compared to the sarcoidosis which showed a significant increase in CD4/CD8 ratio, as compared to the other ILDs [26•].

BAL findings in ILDs according to the disease

BAL cell counts and differential are highly suggestive or may even have diagnostic of certain ILDs entities (Table 2). Many clinicians routinely perform BAL analysis as an essential component of workup of patients presenting with new-onset ILD. In fact, BAL cellular analyses are an advantageous method in restricting the differential diagnoses of ILDs.

Table 2 ILDs according to cellular patterns found by BAL

BAL cellular pattern	Possible diagnosis
Eosinophils >25 %	Eosinophilic pneumonia, drug-induced pneumonitis, tropical pulmonary eosinophilia, fungal infection bronchopulmonary aspergillosis, Churg-Straus syndrome, acute eosinophilic pneumonia, chronic eosinophilic pneumonia, parasitic infection.
Lymphocytes (>30 %)	Sarcoidosis, HP, NSIP, drug reaction, LIP, lymphoma and other lymphoproliferative disorder.
Lymphocytes (15 to 30 %)	IPF, COP, PLHC and may be other IIP.
Neutrophils	AIP, DAD, Acute exacerbation-IPF, pulmonary infection pulmonary haemorrhage- DAH.
Squamous epithelial cells >5 %	Unsuitable sample due to upper airway secretion contamination
Bronchial epithelial cells >5 %	Sample may be unsuitable for cell analysis

IPF

It is critical to evaluate patients with suspected IPF for potential chronic hypersensitivity pneumonitis; as such, patients may simulate IPF. Lymphocytosis of 40 % or higher in BAL may prompt the treating clinician to look for occult hypersensitivity pneumonitis, provoking further examination for environmental insults, and even consideration of surgical lung biopsy.

Increasing knowledge of the classical HRCT findings of specific features that are associated with UIP histopathological pattern obviate the need for lung biopsy in the diagnosis of IPF [27•]. BAL findings, although non-specific to IPF, are distinct from differential cell counts in sarcoidosis or HP, but it is difficult to differentiate fibrotic NSIP from IPF. This was reported in another evidence stated that BAL had neither a diagnostic role nor prognostic value with either IPF or NSIP [28].

More recent study examined hepatocyte growth factors (HGF) that were elevated in BAL from IPF in non-smokers patients. HGF levels positively correlated with TGF-beta BAL concentration, while negatively with vital capacity, neutrophils and BAL lymphocytes [29].

NSIP

Several studies have reported a lymphocytic BAL in patients with non-specific interstitial pneumonia (NSIP), although others have not established this. In a study that compared BAL cell counts from 19 patients with fibrotic NSIP and 35 patients with IPF, no compelling disparity was established in the frequencies of cells [30]. Further data presented that among 74 patients with IPF cases diagnosed by the clinical and HRCT findings, the only patients that were identified to have a non-IPF diagnosis such as HP and NSIP had a BAL lymphocytosis of >30 % [31]. Additionally, a retrospective observational study evaluated the role of BAL in recognition of NSIP from UIP in a number of patients, and they observed that UIP was characterized by a higher neutrophil count (7 %) and lower lymphocyte count (5 %) than NSIP [30, 32].

HP

BAL is a sensitive method for suspected cases of hypersensitivity pneumonitis. A marked lymphocytosis more than 50 % is a non-specific but helpful marker. BAL lymphocytosis up to 50 % may raise a suspicion for the diagnosis of HP and patients with HP [7]. More recent data show that periodic acid-Schiff (PAS)-positive cells were significantly reduced in HP compared to IPF and sarcoidosis but no significant correlation between PAS positive cells and inflammatory cells was noticed [32, 33]. Another study found that plasma cells are absent from normal BAL, but their presence accompanied by "foamy macrophages" and raised lymphocyte count is highly suggestive of either HP or drug toxicity [33]. Other ILDs associated with the existence of plasma cells in BAL include cryptogenic organizing pneumonia and chronic eosinophilic pneumonia. Mast cells have been involved in the pathogenesis of lung inflammation and fibrosis. An increased number of mast cells in BAL have been observed in IPF, HP, and, to a much lesser degree, in sarcoidosis, and seems to relate to advanced or progressive disease [34].

COP

BAL findings in cryptogenic organizing pneumonia (COP) are characterized by increases in the overall number of lymphocytes, neutrophils, eosinophils and macrophages. But the lymphocytic cellular pattern was reported as the most prominent type of cells with mild raising in neutrophils and eosinophils. The CD4/CD8 ratio is usually normal or low [14, 15].

CTDs

Although BAL fluid analysis has been performed in all of the connective tissue diseases (CTDs), the presence or absence of alveolitis has been described to reflect local inflammation, in which neutrophils and eosinophils are predominant. In CTD-ILDs, BAL neutrophilia seems to correlate with poorer lung function but has not consistently proved useful for diagnosis or assessing prognosis and response to therapy [35, 36].

Despite these issues, BAL is an important adjunct in the evaluation of radiographic abnormalities, primarily in ruling out alternative diagnoses to CTD-ILD, including eosinophilia observed in some drug reactions, diffuse alveolar haemorrhage and opportunistic infection [37]. BAL has a restricted role in the diagnosis and checking of connective tissue diseases affecting the lung [14, 15]. However, bronchoscopy with BAL should be considered in the evaluation of new infiltrates in any patient receiving immunosuppressive therapy. BAL analysis showed that the counts of lymphocytes and eosinophils were meaningfully higher in DM-ILD than in PM-ILD [38].

SS

BAL has giving important diagnostic and prognostic information regarding the s of systemic sclerosis (SS)-ILD [39, 40]. ILD progression was related with the presence of honeycombing on HRCT, with the existence of eosinophils, with low CD4/CD8 ratio. Presence of an increase number of neutrophils, eosinophils and alveolar macrophages was reported in SS-ILD patients [41] Based on current data, BAL is not recommended for repetitive assessment and management of SS-ILD [42].

Sarcoidosis

In sarcoidosis; BAL lymphocyte count and percentage are elevated, while the neutrophil and eosinophil percentages are normal [43]. Sarcoidosis is highly suspected when lymphocytes ranged 30–50 % and neutrophils count is low [14, 15]. T lymphocytes with an elevated CD4/CD8 ratio is an important clue for the diagnosis of sarcoidosis [44]. The CD103+CD4+/CD4+ ratio has been postulated as a possible diagnostic indicator for sarcoidosis [45]. The finding of a raised neutrophil count in sarcoidosis appears to correlate with a more severe disease and may indicate need for treatment [45].

Drug-induced ILDs

Drugs history is very important in the approach to ILD patients as many drugs have been connected with interstitial lung disease such as nitrofurantoin, chemotherapeutic agents and amiodarone [46]. The diagnosis is usually problematic and difficult to confirm. BAL may be of use in determining the existence of pneumonitis or any drug-related lung injury. It may also be of value in ruling out other disease or complications (e.g. vasculities, alveolar haemorrhage, lymphangitic carcinomatosis or infection) that are widespread when chemotherapeutic agents are employed [47].

Most drug-induced immunological reactions and the most noticeable feature of BAL in drug-induced lung injuries was a lymphocytic alveolits, either pure or with neutrophil and/or eosinophilic alveolits along with an inequity in T lymphocyte [48]. As such, HP and COP secondary to drug reaction may be ruled out if BAL cytology is normal. In MTX-induced pneumonitis, CD4+ cells may also increase; this elevation has also been demonstrated with many other drugs such as sirolimus, nitrofurantoin and ampicillin [49].

Another data reporting that monoclonal antibodies which used as a targeted therapy for a variety of diseases have been associated with ILDs in the treated patients. Investigators found that mixed inflammation with moderate lymphocytic and mild neutrophilic alveolitis is the most common BAL cellular pattern in patients with ILD. Such findings may be useful for the early identification of monoclonal antibodies-ILD [50].

Other differential diagnosis for ILDs

Diffuse alveolar haemorrhage-DAH

BAL is helpful in diagnosing alveolar haemorrhage, including Wegener's granulomatosis, Good pasture's syndrome, systemic lupus erythematosus and other vasculitides. In the absence of coagulopathy, the gross appearance of increasingly haemorrhagic returns of the BAL fluid in sequential aliquots and/or the presence of hemosiderin-laden macrophages which may be present more than 48 h after the onset of pulmonary haemorrhage [51].

AEP

Acute eosinophilic pneumonia (AEP) is an acute pneumonitis with marked eosinophils in the lungs. The majority of patients present with diffuse, mixed alveolar and interstitial reticular infiltrates. However, at initial presentation, the chest radiograph may only present slight reticular opacities and then

gradually progress to mixed diffuse alveolar or interstitial infiltrate. Characteristically BAL eosinophills are more than 25 %. The differential diagnosis involves other eosinophilc pulmonary diseases, drug-provoked pneumonitis, fungal infection and Churg-Straus syndrome.

CEP

CEP is a disorder characterized by sub-acute symptoms of dyspnoea and bilateral peripheral air-space diseases or a patchy infiltrates labelled as the "hotographic negative" of pulmonary oedema in chest radiography. In a patient with compatible clinical presentation and a BAL eosinophill count >40% is strongly suggestive of CEP.

Chronic micro-aspiration with gastroesophageal reflux

Chronic aspiration should be suspected in patients with recurrent pneumonias or in patients with unexplained interstitial opacities. When chronic aspiration is a concern, BAL should be collected from the most involved lung segments as directed by chest radiographs (normally the lower lung zones).

BAL cellularity is usually high and predominantly lymphocytes, eosinophils and macrophages. The existence of sizeable numbers of lipid-laden macrophages is a diagnostic finding of chronic aspiration or lipoid pneumonia [52]. Multinucleated giant cells may be seen in BAL and often contain lipid droplets within their cytoplasm [53].

Summary and conclusions

- Bronchoalveolar lavage (BAL) is a considerable safe and minimally invasive procedure to obtain sample alveolar cells with very low morbidity and mortality.
- The interpretation of BAL samples should be done in the framework of clinical and radiological data, and the standardized techniques for collecting and analysing BAL fluid are needed.
- BAL is non-specific in the evaluation of ILDs but may be helpful to narrow the differential diagnosis.
- The diagnostic usefulness of BAL in idiopathic pulmonary fibrosis is limited.
- In pulmonary sarcoidosis, the BAL lymphocyte total is increased, while the neutrophil and eosinophill counts are normal. The CD4/CD8 T lymphocyte ratio (>2) is characteristically increased in active disease but may decreased in more advance disease.
- In hypersensitivity pneumonitis, BAL characteristically shows a marked lymphocytosis and a low CD4/CD8 ratio.
- There are inconsistencies in the BAL cytology among various ILDs, including non-specific interstitial pneumonia, idiopathic pulmonary fibrosis, connective tissue disease-related ILD, cryptogenic organizing pneumonia and drug-induced ILD. In these diseases, the purpose of BAL is mainly to rule out other infectious or malignant conditions.

Compliance with Ethics Guidelines

Conflicts of Interest The authors declare that they have no conflicts of interests related to the material.

Human and Animal Rights and Informed Consent This article contains no studies with human or animal subjects performed by the author.

References

Papers of particular interest, published recently, have been highlighted as:
• Of importance
•• Of major importance

1. Kilinc G, Kolsuk EA. The role of bronchoalveolar lavage in diffuse parenchymal lung diseases. Curr Opin Pulm Med. 2005;11(5):417–21.
2. American Thoracic S, European RS. American Thoracic Society/European Respiratory Society International Multidisciplinary Consensus Classification of the Idiopathic Interstitial Pneumonias. This joint statement of the American Thoracic Society (ATS), and the European Respiratory Society (ERS) was adopted by the ATS board of directors, June 2001 and by the ERS Executive Committee, June 2001. Am J Respir Crit Care Med. 2002;165(2):277–304.
3.•• Meyer KC, Raghu G, Baughman RP, Brown KK, Costabel U, du Bois RM, et al. An official American Thoracic Society clinical practice guideline: the clinical utility of bronchoalveolar lavage cellular analysis in interstitial lung disease. Am J Respir Crit Care Med. 2012;185(9):1004–14. **This is ATS guideline written by experts in the interstitial pulmonary disease. Very comprehensive explain the findings of BAL in ILD also discuses other aspect of technical aspect of BAL procedures. It is very essential for all pulmonologist to read.**
4. Report of the European Society of Pneumology Task Group on BAL. Clinical guidelines and indications for bronchoalveolar lavage (BAL). Eur Respir J. 1990;3(8):937–76.
5. Kanne JP. Interstitial lung disease (ILD): imaging finding, and the role of imaging in evaluating the patient with known or suspected ILD. Semin Roentgenol. 2010;45(1):3.
6. Credle Jr WF, Smiddy JF, Elliott RC. Complications of fiberoptic bronchoscopy. Am Rev Respir Dis. 1974;109(1):67–72.
7. Costabel U, Guzman J. Bronchoalveolar lavage in interstitial lung disease. Curr Opin Pulm Med. 2001;7(5):255–61.
8.•• Baughman RP. Technical aspects of bronchoalveolar lavage: recommendations for a standard procedure. Semin Respir Crit Care Med. 2007;28(5):475–85. **This review article is very important, it summarizes all previous the recommendations and discusses the variable effects they have on BAL results it also provide a**

standard methodology that can be used by the largest number of pulmonologists.

9. Martin TR, Raghu G, Maunder RJ, Springmeyer SC. The effects of chronic bronchitis and chronic air-flow obstruction on lung cell populations recovered by bronchoalveolar lavage. Am Rev Respir Dis. 1985;132(2):254–60.
10. The BAL Cooperative Group Steering Committee. Bronchoalveolar lavage constituents in healthy individuals, idiopathic pulmonary fibrosis, and selected comparison groups. Am Rev Respir Dis. 1990;141((5 Pt 2):S169–202.
11. Meyer KC. Bronchoalveolar lavage as a diagnostic tool. Semin Respir Crit Care Med. 2007;28(5):546–60.
12. Reynolds HY. Use of bronchoalveolar lavage in humans—past necessity and future imperative. Lung. 2000;178(5):271–93.
13.•• Meyer KC, Raghu G. Bronchoalveolar lavage for the evaluation of interstitial lung disease: is it clinically useful? Eur Respir J. 2011;38(4):761–9. **This is a Very useful review of how to use BAL as a diagnostic tool for the diagnosis of ILD it mentioned briefly the therapeutic role of BAL but not in details. It is short and up to the point.**
14. Welker L, Jorres RA, Costabel U, Magnussen H. Predictive value of BAL cell differentials in the diagnosis of interstitial lung diseases. Eur Respir J. 2004;24(6):1000–6.
15. Domagala-Kulawik J, Skirecki T, Maskey-Warzechowska M, Grubek-Jaworska H, Chazan R. Bronchoalveolar lavage total cell count in interstitial lung diseases—does it matter? Inflammation. 2012;35(3):803–9.
16. Daniele RP, Elias JA, Epstein PE, Rossman MD. Bronchoalveolar lavage: role in the pathogenesis, diagnosis, and management of interstitial lung disease. Ann Intern Med. 1985;102(1):93–108.
17. Kantrow SP, Meyer KC, Kidd P, Raghu G. The CD4/CD8 ratio in BAL fluid is highly variable in sarcoidosis. Eur Respir J. 1997;10(12):2716–21.
18. Drent M, van Nierop MA, Gerritsen FA, Wouters EF, Mulder PG. A computer program using BALF-analysis results as a diagnostic tool in interstitial lung diseases. Am J Respir Crit Care Med. 1996;153(2):736–41.
19. Schnabel A, Richter C, Bauerfeind S, Gross WL. Bronchoalveolar lavage cell profile in methotrexate induced pneumonitis. Thorax. 1997;52(4):377–9.
20. Laviolette M, Cormier Y, Loiseau A, Soler P, Leblanc P, Hance AJ. Bronchoalveolar mast cells in normal farmers and subjects with farmer's lung. Diagnostic, prognostic, and physiologic significance. Am Rev Respir Dis. 1991;144(4):855–60.
21. Nagai S, Kitaichi M, Itoh H, Nishimura K, Izumi T, Colby TV. Idiopathic nonspecific interstitial pneumonia/fibrosis: comparison with idiopathic pulmonary fibrosis and BOOP. Eur Respir J. 1998;12(5):1010–9.
22. Meyer KC. The role of bronchoalveolar lavage in interstitial lung disease. Clin Chest Med. 2004;25(4):637–49.
23. Bradley B, Branley HM, Egan JJ, Greaves MS, Hansell DM, Harrison NK, et al. Interstitial lung disease guideline: the British Thoracic Society in collaboration with the Thoracic Society of Australia and New Zealand and the Irish Thoracic Society. Thorax. 2008;63(5):v1–v58.
24. Pesci A, Bertorelli G, Manganelli P, Mori PA, Strinati F, Marangio E, et al. Bronchoalveolar lavage in chronic eosinophilic pneumonia. Analysis of six cases in comparison with other interstitial lung diseases. Respiration. 1988;54(1):16–22.
25. Hesselstrand R, Wildt M, Bozovic G, Andersson-Sjoland A, Andreasson K, Scheja A, et al. Biomarkers from bronchoalveolar lavage fluid in systemic sclerosis patients with interstitial lung disease relate to severity of lung fibrosis. Respir Med. 2013;107(7):1079–86.
26.• Lee W, Chung WS, Hong KS, Huh J. Clinical usefulness of bronchoalveolar lavage cellular analysis and lymphocyte subsets in diffuse interstitial lung diseases. Ann Lab Med. 2015;35(2):220–5. **This study examine usufulness of lymphocytes subset of BAL analysis in the dignaosis of diffuse interstitial pneumonia. It concluse that examining lymphocyes subset is not benficial except for sarcoidosis and eosinphilic pneumonia.**
27.• Flaherty KR, King Jr TE, Raghu G, Lynch 3rd JP, Colby TV, Travis WD, et al. Idiopathic interstitial pneumonia: what is the effect of a multidisciplinary approach to diagnosis? Am J Respir Crit Care Med. 2004;170(8):904–10. **Mutidisciplinary approach for Idiopathic interstitial pneumonia is very crucial. This study is about the effect of a multidisciplinary approach to diagnosis of Idiopathic interstitial pneumonia. It conclude that dynamic interactions between clinicians, radiologists, and pathologists improve interobserver agreement and diagnostic confidence.**
28. Veeraraghavan S, Latsi PI, Wells AU, Pantelidis P, Nicholson AG, Colby TV, et al. BAL findings in idiopathic nonspecific interstitial pneumonia and usual interstitial pneumonia. Eur Respir J. 2003;22(2):239–44.
29. Przybylski G, Chorostowska-Wynimko J, Dyczek A, Wedrowska E, Jankowski M, Szpechcinski A, et al. Studies of hepatocyte growth factor (HGF) in bronchoalveolar lavage (BAL) in chronic interstitial lung diseases (ILDs). Pol Arch Med Wewn. 2015
30. Ryu YJ, Chung MP, Han J, Kim TS, Lee KS, Chun EM, et al. Bronchoalveolar lavage in fibrotic idiopathic interstitial pneumonias. Respir Med. 2007;101(3):655–60.
31. Lynch DA, Rose CS, Way D, King Jr TE. Hypersensitivity pneumonitis: sensitivity of high-resolution CT in a population-based study. AJR Am J Roentgenol. 1992;159(3):469–72.
32. Hauber HP, Zabel P. PAS staining of bronchoalveolar lavage cells for differential diagnosis of interstitial lung disease. Diagn Pathol. 2009;4:13.
33. Drent M, van Velzen-Blad H, Diamant M, Wagenaar SS, Donckerwolck-Bogaert M, van den Bosch JM. Differential diagnostic value of plasma cells in bronchoalveolar lavage fluid. Chest. 1993;103(6):1720–4.
34. Pesci A, Bertorelli G, Gabrielli M, Olivieri D. Mast cells in fibrotic lung disorders. Chest. 1993;103(4):989–96.
35. Garcia JG, James HL, Zinkgraf S, Perlman MB, Keogh BA. Lower respiratory tract abnormalities in rheumatoid interstitial lung disease. Potential role of neutrophils in lung injury. Am Rev Respir Dis. 1987;136(4):811–7.
36. Komocsi A, Kumanovics G, Zibotics H, Czirjak L. Alveolitis may persist during treatment that sufficiently controls muscle inflammation in myositis. Rheumatol Int. 2001;20(3):113–8.
37. Ramirez P, Valencia M, Torres A. Bronchoalveolar lavage to diagnose respiratory infections. Semin Respir Crit Care Med. 2007;28(5):525–33.
38. Fujisawa T, Suda T, Nakamura Y, Enomoto N, Ide K, Toyoshima M, et al. Differences in clinical features and prognosis of interstitial lung diseases between polymyositis and dermatomyositis. J Rheumatol. 2005;32(1):58–64.
39. Kowal-Bielecka O, Kowal K, Highland KB, Silver RM. Bronchoalveolar lavage fluid in scleroderma interstitial lung disease: technical aspects and clinical correlations: review of the literature. Semin Arthritis Rheum. 2010;40(1):73–88.
40. De Santis M, Bosello SL, Peluso G, Pinnelli M, Alivernini S, Zizzo G, et al. Bronchoalveolar lavage fluid and progression of scleroderma interstitial lung disease. Clin Respir J. 2012;6(1):9–17.

41. Silver RM, Metcalf JF, Stanley JH, LeRoy EC. Interstitial lung disease in scleroderma. Analysis by bronchoalveolar lavage. Arthritis Rheum. 1984;27(11):1254–62.
42. Behr J, Vogelmeier C, Beinert T, Meurer M, Krombach F, Konig G, et al. Bronchoalveolar lavage for evaluation and management of scleroderma disease of the lung. Am J Respir Crit Care Med. 1996;154(2 Pt 1):400–6.
43. Drent M, Mansour K, Linssen C. Bronchoalveolar lavage in sarcoidosis. Semin Respir Crit Care Med. 2007;28(5):486–95.
44. Danila E, Norkuniene J, Jurgauskiene L, Malickaite R. Diagnostic role of BAL fluid CD4/CD8 ratio in different radiographic and clinical forms of pulmonary sarcoidosis. Clin Respir J. 2009;3(4): 214–21.
45. Kolopp-Sarda MN, Kohler C, De March AK, Bene MC, Faure G. Discriminative immunophenotype of bronchoalveolar lavage CD4 lymphocytes in sarcoidosis. Lab Investig. 2000;80(7):1065–9.
46. Vahid B, Marik PE. Pulmonary complications of novel antineoplastic agents for solid tumors. Chest. 2008;133(2):528–38.
47. Costabel U, Uzaslan E, Guzman J. Bronchoalveolar lavage in drug-induced lung disease. Clin Chest Med. 2004;25(1):25–35.
48. Akoun GM, Cadranel JL, Rosenow EC, Milleron BJ. Bronchoalveolar lavage cell data in drug-induced pneumonitis. Allergy Immunol. 1991;23(6):245–52.
49. Costabel U, Guzman J, Bonella F, Oshimo S. Bronchoalveolar lavage in other interstitial lung diseases. Semin Respir Crit Care Med. 2007;28(5):514–24.
50. Gupta S, Smith P, Twigg Iii HL, Hage CA. Bronchoalveolar lavage cellular patterns in monoclonal antibody-induced lung disease. Respiration. 2014;88(3):185–9.
51. Sherman JM, Winnie G, Thomassen MJ, Abdul-Karim FW, Boat TF. Time course of hemosiderin production and clearance by human pulmonary macrophages. Chest. 1984;86(3):409–11.
52. Corwin RW, Irwin RS. The lipid-laden alveolar macrophage as a marker of aspiration in parenchymal lung disease. Am Rev Respir Dis. 1985;132(3):576–81.
53. Lauque D, Dongay G, Levade T, Caratero C, Carles P. Bronchoalveolar lavage in liquid paraffin pneumonitis. Chest. 1990;98(5):1149–55.