Table 1. – Consequences and side effects of BAL

Alveolar infiltration	<10% of cases, usually subside after 48 hours[§]	7, 8, 9
Crackles	withing 24 hours over dependent areas[§§]	5, 10
Wheezing	in hyperreactive patients up to 1–2 weeks	4
Bronchospasm	rarely in normoreactive, more frequent in hyperreactive patients	4, 5, 9
Fever	10–30%, some hours after BAL[§§]	7, 8, 11, 12, 14
Lung function	transient decrease of FEV_1, VC, PEF, Po_2[§§, $, $$]	5, 11, 12, 13, 14, 15, 16, 17, 18
	transient rise of Pco_2 in patients with COPD	19
Bronchial Reactivity	no change after BAL	15, 20
Epithelial integrity	no effect on lung epithelial permeability 24 hours after BAL	21
	transient decrease of ciliary beat frequency	2
Bleeding	insignificant	9

§: Risk increases with size of instilled lavage fluid volume and numbers of lavaged segments; §§: Risk increases with volume of instilled lavage volume; $: More likely in hyperreactive patients or in patients with severe underlying infiltrative lung diseases; $$: Supplemental oxgyen prevents hypoxemia during BAL.

The clinical role of BAL in idiopathic pulmonary fibrosis

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The aim of this paper is to review the literature on the clinical value of bronchoalveolar lavage (BAL) in the diagnosis and management of patients with idiopathic pulmonary fibrosis (IPF) (synonym: cryptogenic fibrosing alveolitis). This topic has been included in a number of recent detailed reviews [22–24]]. IPF is one of the most serious interstitial lung diseases. The prognosis is poor, with a mean survival of only 3–5.6 yrs [25–27], but progression is very variable in individual patients. Objective response to corticosteroids is achieved in only about 20% of cases [25, 26, 28], and prognostic factors associated with favourable response are younger age, shorter duration of disease [27–29], and more cellular lung biopsies [26, 30, 31]. Thus, it is important to achieve diagnosis and start treatment as soon as possible.

Diagnostic value of BAL in IPF

There are no specific diagnostic BAL features in IPF, but useful information can be provided by the differential counts of BAL cells, and the profile of BAL cell types. Different types of increased BAL cells predominate in the different interstitial lung diseases, which do not provide a definitive diagnosis because of variation within, and overlap between, disorders but trends of difference between the disorders can support the provisional diagnosis or suggest an alternative.

Neutrophils are the main lavage cell type increased in IPF [32–34] and in other diffuse interstitial fibrosing lung disorders including fibrosing alveolitis associated with collagen vascular diseases (see below), the inorganic dust disease asbestosis [35], and experimental models of silicosis [36]. Patients with IPF, collagen vascular diseases, and asbestosis also frequently have increased eosinophils in lavage [34–38]. Apart from this, high counts of eosinophils in lavage have only been reported in cases of eosinophilic pneumonia, in patients with Churg-Strauss syndrome and in patients with in asthma [39].

The most useful aid to diagnosis is given by the full profile of BAL cell types increased in each patient. The combination of increased neutrophils and eosinophils occurs in about two-thirds of patients with

IPF [34, 40] and in asbestosis [35], but is very rare in patients with granulomatous lung diseases where lymphocytes are the predominant increased BAL cell type. Furthermore, the distinction between IPF and asbestosis is aided by the identification of asbestos bodies amongst the lavage cells, which indicate that exposure has taken place and that the diagnosis of occupational lung disease must be considered [25, 35, 41]. Lone neutrophil increases occur in many patients with IPF but caution must be taken regarding the diagnostic interpretation, since moderate increases can arise for many reasons, and very high counts occurring alone can suggest bacterial infection. However, it is of interest that neutrophil counts increase and lymphocyte counts tend to fall as the grade of radiographic shadowing and fibrosis increases in patients with sarcoidosis [42–44].

A minority of IPF patients show a less typical BAL cell profile. In particular, the subset who respond favourably to corticosteroids frequently have slight to moderate increases in BAL lymphocytes in association with neutrophils but very rarely with eosinophils [34, 45–47]. Increases in BAL lymphocytes have also been reported in workers exposed to asbestos or silica at a stage prior to the development of symptoms [48, 49].

Increased T-helper/suppressor BAL lymphocyte ratios have recently been reported in IPF, contrasting with reduced ratios in patients with associated collagen vascular diseases [50, 516], but the diagnostic value of this approach is restricted since increases in BAL lymphocytes are relatively infrequent in these diseases. Measurement of carcinoembryonic antigen in BAL fluid has recently been claimed to be a possible marker of early malignant change in the clinical course of IPF [52]. Physicians should also be aware that alveolar lipoproteinosis can very occasionally develop in patients with IPF following treatment with corticosteroids [53]. It is also important to be aware that findings similar to those in patients with IPF have recently been reported in clinically unaffected family members, namely increased numbers of neutrophils, evidence of macrophage activation, and growth factors for lung fibroblasts [54].

In conclusion, inclusion of lavage in the pre-treatment investigation of patients with IPF, although it is not pathognomonic, can give some support to the diagnosis, when considered in the full clinical context. However, once patients have commenced therapy this can influence the lavage findings (see below).

Prognostic value of BAL in IPF

Pre-treatment BAL cell counts may be of some value in the clinical management of IPF patients as a prognostic indicator of response to therapy.

Patients with increased percentage counts of BAL lymphocytes have a significantly better chance of responding to corticosteroids than the remainder [34, 45–47]. By contrast, percentages of neutrophils and eosinophils are significantly higher in those who fail to respond to steroids [34, 45, 55] and patients with increased eosinophils have an especially poor response [34, 40, 45, 46, 56, 57]. However, there is a recent report that some patients with increased eosinophils can respond to cyclophosphamide (100 mg per day) combined with prednisolone (20 mg per alternate day) [58]. It is hoped that future prospective trials may show that pre-treatment lavage cell counts may be of value to indicate the most appropriate drug for the individual patient.

Numerous other markers can be measured in BAL samples, but there is little information on their correlations with clinical features. It has recently been reported that IPF patients with high concentrations of myeloperoxidase [59], and those with higher levels of hyaluronate and type III procollagen peptide [60] in BAL fluid deteriorate more rapidly than those with low levels; that patients with increased histamine in BAL fluid have higher grades of fibrosis in their lung biopsies [41]; and that patients with late stage IPF have low levels of proteolytic activity in the BAL fluids [62]. Factors released from activated alveolar macrophages may play the major role in stimulating the growth of fibroblasts in IPF [63], but the clinical value of measuring such markers is unknown. However, since colchicine can suppress the production of these factors *in vitro*, it has been suggested that this drug may have a potential role in the treatment of IPF [64].

In conclusion, the current evidence on the prognostic value of lavage findings in IPF suggests that the information may be of some value in guiding the selection of therapeutic agents.

The value of BAL in monitoring and surveillance of therapy in IPF

The safety of BAL makes it an ideal technique to monitor changes occurring with disease progression and under the influence of therapy, but there is still relatively little information on serial lavage studies in patients with IPF. One series of patients has been followed from 1–7 yrs, mean 4 yrs [58]. Patients responding to high dose prednisolone showed a significant fall in the percentages of all inflammatory cell types, but most notably in neutrophils, while counts remained elevated or increased in the non-responders; patients followed on treatment with cyclophosphamide plus low dose prednisolone, showed a significant fall in eosinophils in the responders, but not in the non-responders. Another study has also found that corticosteroid treatment does not suppress BAL neutrophils in non-responders after 3 mths or 6 mths of therapy, but stated that patients failing to respond to cyclophosphamide alone or plus corticosteroids showed a significant reduction in neutrophils at 3 mths and at 6 mths [65]. By contrast, a third study has observed that BAL neutrophil counts increased after 3 mths prednisolone in smokers, but not in nonsmokers, with IPF who showed clinical improvement [66]. However, the follow-up periods were very different in the three studies, up to 7

yrs in the former [58], but only 3 mths [65, 66] and 6 mths [65] in the latter. Thus, it is still premature to draw conclusions on the clinical value of lavage cell counts in monitoring the progress of IPF patients.

Serial lavage studies have also recently shown that proportions of phosphatidylglycerol, which are reduced in the BAL fluids of many untreated IPF patients [67, 68], return to normal in patients responding to prednisolone but not in non-responders [67]. It has been suggested that such changes may reflect the extent of damage to the alveolar epithelium in IPF.

In conclusion, preliminary reports indicate that BAL may be of clinical value to monitor changes in the lungs associated with therapeutic response in IPF, but further information is required. In particular, independent prospective studies are needed where patients are evaluated over comparable long-term periods, and details are required of survival as well as radiological and functional response to therapy.

Conclusions

Current published evidence suggests that lavage is of value to aid the diagnosis and management of patients with IPF. BAL cell counts are only a guide to the differential diagnosis of IPF because of the variability within and overlap between diseases. Nevertheless, BAL is of particular value to identify and exclude some of the rarer lung diseases which must be considered in the provisional diagnosis. BAL can provide some useful prognostic indicators in IPF which may aid therapeutic decisions, and serial BAL measurements may have a place in assessing suppression of inflammation in patients responding to therapy. However, at this stage in our knowledge caution should be given to the interpretation of BAL findings, and they are most useful when considered and interpreted in the context of the overall clinical and other investigatory techniques used in the diagnosis and management of patients with this serious lung disease.

Collagen-vascular diseases

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Inflammatory processes that develop in the lung in many of the collagen vascular diseases (CVD) usually result in a diffuse interstitial lung disease (ILD) similar to idiopathic pulmonary fibrosis. Chronic alveolitis, as assessed by bronchoalveolar lavage, revealed the same characteristic pattern of alveolar inflammation associated with idiopathic pulmonary fibrosis; which is evidence of neutrophil accumulation and macrophage activation [38, 45, 50, 69–85]. However, there is a considerable overlap for each disease and type of alveolitis. In addition, inflammatory alveolitis may also be present in a high proportion of patients with CVD and without clinical or radiological evidence of pulmonary involvement, suggesting the presence of an ongoing subclinical alveolitis.

Cellular characteristics of alveolitis

Total number of recovered cells is increased in patients with overt ILD but not in patients without ILD. In addition, total number of cells is progressively reduced in advanced progressive systemic sclerosis [77]. The distribution of BAL cell type according to the disease and to the presence of an associated ILD is summarized in table 1. In addition, alveolar macrophages are "spontaneously" activated and release various bioactive mediators that could be relevant to the pathogenesis of ILD: superoxide anion (various CVD), neutrophil chemotactic factors (various CVD), fibronectin (various CVD), alveolar macrophage derived growth factor for fibrosis (AMDGF) (progressive systemic sclerosis) and tumour necrosis factor (TNF) (rheumatoid arthritis).

It appears that symptomless patients with CVD can have a similar pattern of alveolar inflammation including accumulation of neutrophils and/or lymphocytes and activated alveolar macrophages [86–91].

On the other hand, some cell activities may be defective: since decreased antibacterial activity of alveolar macrophages has been reported in systemic lupus erythematosus but not in other CVD [92, 93].

Biochemical characteristics of alveolitis

The biochemical analysis of BAL fluid shows an increased transudation of serum factors and/or an increased secretion of mediators: albumin, immunoglobulin G (IgG), IgM, alpha-2 macroglobulin, plasminogen activator, procollagen peptide (progressive systemic sclerosis), collagenase, elastase [73, 76, 83, 84, 94, 95]. So far, the value of biochemical analysis of BAL fluid in diagnosis and management of ILD CVD remains to be established.

Clinical significance of alveolitis in CVD

Since alveolar inflammation is a characteristic feature of CVD patients with or without associated ILD, the BAL cytology is by no means a reliable argument for the diagnosis of ILD in this context. However, BAL may be useful for the diagnosis of an associated