Clinical guidelines and indications for bronchoalveolar lavage (BAL): Report of the European Society of Pneumology Task Group on BAL

Edited by H. Klech* and C. Hutter

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Introduction

As for many clinical tools, there is at the present time no clear agreement on the appropriate clinical use of BAL. Undoubtedly, the recent and encouraging clinical experiences with BAL for diagnosis of opportunistic infections in the immunocompromised patient have encouraged a universal acceptance and interest in BAL. Because of the low morbidity of the lavage procedure and the significant yield of clinically important information, many physicians have been encouraged to perform a lavage during bronchoscopies undertaken for a variety of indications. This has resulted in a considerable body of experience with BAL in a number of clinical settings. For many years, one of the main obstacles for general acceptance of BAL as a clinical tool has been the vast disparity among centres worldwide regarding the technique and the processing of the BAL material.

In order to address this important issue of standardization the European Society of Pneumology (SEP), in 1988, set up a Task Force on Bronchoalveolar Lavage. The first report of the group focused specifically on technical recommendations and guidelines on how to perform BAL and how to process BAL material and was published in 1989 in this journal [1].

This is the second joint report of the SEP Task Group on BAL and gives appropriate guidelines and information about the clinical indications and use of BAL in various diseases of the lung. The members of the Task Group have collected all relevant information so far available about the clinical usefulness and indications of BAL. As a result of a critical review of the material and with the help of two consensus conferences of the group this state-of-the-art paper has been produced. It was the aim of the group to provide a short and informative report for the use of clinicians. Thus, this report is not intended as a comprehensive review of each of the topics. It provides guidelines and recommendations about the clinical value of BAL for diagnosis, for prediction of prognosis, and gives some comparative evaluation of BAL to other established investigative means. Only the pertinent literature for these issues is referenced. A small chapter deals with therapeutic applications of bronchial lavage or bronchoalveolar lavage.

Because the field of BAL worldwide is so rapidly evolving and the application of BAL is so widespread, this report can only give recommendations and guidelines, and should not be regarded as an "indication book". There will be several centres where a special expertise for diagnostic applications of BAL has been accomplished which will regard our recommendations as being too restrictive; and there will be other centres also which are still in a learning and experimental stage regarding the clinical use and performance of BAL. Therefore, our Task Group tried to meet the understanding and the requirements of most of the centres currently performing BAL and to give a fair balance regarding our clinical recommendations.

H. Klech

Side-effects and safety of BAL

H. Klech and C. Hutter

Today, BAL is regarded as a very safe procedure. Side-effects are more or less comparable to regular fibrebronchoscopy unless specific invasive procedures like transbronchial lung biopsy are performed. The overall complication rate with BAL is reported to be 0-3% in comparison to 7% with transbronchial lung biopsy and 13% when using open lung biopsy [2]. So far no lethal complication directly attributable to BAL has been reported. Lethality for transbronchial biopsy is reported to be 0.2% and for open lung biopsy 1.8% [2].

Minor side-effects of BAL include coughing during lavage, fever and chills some hours after lavage (which can usually be treated with the help of simple antipyretics), transient alveolar infiltration in the dependent lung segment 24 h after the procedure, transient deterioration of lung function parameters like vital capacity, forced expiratory volume in one second (FEV1), decrease of oxygen tension (Po2) (consequences of saline lavage are expressed more in patients with underlying pulmonary diseases in comparison to healthy volunteers). Most side-effects reported are closely related to endoscopic technique, location and extent of lavaged lung area, volume and temperature of instilled fluid (summary in table 1).

Supplemental oxygen delivery as well as ear oximetry and electrocardiogram (ECG) monitoring is strongly advised in patients with severe underlying diseases or in any other critical condition [3]. Patients with mild asthma have been successfully lavaged [4], however, patients with a history of asthma bronchiale should be handled with special caution and careful monitoring is advised [5, 6]:

1) Supplemental oxygen with a nasal prong should be administered throughout the entire procedure.
2) Premedication with aerosolized beta-agonists.
3) Ear-oximetry and ECG-monitoring.
Lung function transient decrease of FEV₁, VC, PEF, Po₂ 5, 11, 12, 13, 14, 15, 16, 17, 18 transient rise of Pco₂ in patients with COPD 19 no change after BAL 15, 20 no effect on lung epithelial permeability 24 hours after BAL 21 transient decrease of ciliary beat frequency 2 insignifiant 8

§: 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 oxygen prevents hypoxemia during BAL.

The clinical role of BAL in idiopathic pulmonary fibrosis


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 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
Cellularcharacteristicsofalveolitis

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).

Conclusions

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).

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

B. Wallaert, G.A. Rossi, Y. Sibille

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.

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
lung disease (infection, pulmonary haemorrhage, alveolar proteinosis etc.) or of drug-induced lung disorder [96-98]. BAL may also be useful to assess the activity of acute or chronic ILD in patients with scleroderma or with dermatopolymyositis [72, 82, 99]. In general, when increased numbers of lymphocytes are present in BAL fluid, lung disease is associated with a relatively good prognosis, whereas the presence of a predominantly neutrophilic or eosinophilic alveolitis is associated with a higher risk of functional and radiographic deterioration.

The role of BAL in therapeutic decision in symptomless patients with CVD is unclear since its prognostic value is still controversial. Preliminary data suggest that: 1) lymphocyte alveolitis is of good prognosis; 2) neutrophil alveolitis is associated with progressive deterioration of pulmonary function test (PFT) over a 1 yr follow-up in untreated patients. However, corticosteroid treated patients can improve their PFT while the alveolar neutrophilia persists.

In summary:
1) BAL may be useful for the diagnosis of lung complications in CVD; there is as yet no convincing evidence that BAL provides any help in the diagnosis and the management of chronic ILD-CVD.
2) BAL may be useful in the clinical management of acute ILD-CVD.

### Table 1. BAL cytology in collagen vascular diseases

<table>
<thead>
<tr>
<th>Disease</th>
<th>With ILD</th>
<th>Without ILD</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Progressive systemic sclerosis</td>
<td>neutrophils</td>
<td>neutrophils</td>
<td>[38, 70-72, 74, 75, 86]</td>
</tr>
<tr>
<td></td>
<td>eosinophils</td>
<td>eosinophils</td>
<td></td>
</tr>
<tr>
<td>Rheumatoid arthritis</td>
<td>neutrophils</td>
<td>lymphocytes</td>
<td>[76, 79, 83, 85, 86, 90]</td>
</tr>
<tr>
<td></td>
<td>lymphocytes</td>
<td>(CD4+, T5/9)</td>
<td>[78]</td>
</tr>
<tr>
<td>Primary Sjögren syndrome</td>
<td>neutrophils,</td>
<td>lymphocytes</td>
<td>[86-88, 100]</td>
</tr>
<tr>
<td></td>
<td>lymphocytes (CD8+)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systemic lupus</td>
<td>neutrophils</td>
<td>lymphocytes</td>
<td>[92]</td>
</tr>
<tr>
<td>erythematosus</td>
<td>lymphocytes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dermatopolymyositis</td>
<td>neutrophils</td>
<td>neutrophils</td>
<td>[86, 99]</td>
</tr>
<tr>
<td>Mixed connective tissue disease</td>
<td>neutrophils</td>
<td>neutrophils</td>
<td>[86]</td>
</tr>
<tr>
<td>Secondary Sjögren syndrome</td>
<td>neutrophils,</td>
<td>lymphocytes</td>
<td>[86, 88]</td>
</tr>
<tr>
<td></td>
<td>lymphocytes (CD8+)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Presence of ILD is judged by clinical and radiological findings.

The value of bronchoalveolar lavage in the diagnosis and prognosis of sarcoidosis


There is a consensus that BAL changes in sarcoidosis reflect the pathological process [101-110]. Furthermore by analysis of CD4/CD8 lymphocytes BAL can be of benefit in distinguishing sarcoidosis from other granulomatous diseases, such as hypersensitivity pneumonitis [111, 112]. Whether BAL can be used diagnostically and/or prognostically depends, however, on two factors. Firstly, for lavage analysis to be diagnostic, features have to be recorded that together with clinical investigation represent a unique picture of this disease and discriminate it from other interstitial lung diseases. Secondly, there has to be a clear clinical understanding of the level of disease “activity” for the features identified in lavage to be measured against. This second condition is somewhat difficult to satisfy as there appears to be no easy clinical measure of activity. It is only when patients have advanced to fibrotic forms of disease that clear clinical reflections of disease outcome are observed. The values of BAL to diagnosis and prognosis are commented on in tables 1 and 2. Emphasis on the prognostic value of a mere increase of the BAL lymphocyte count, interpreted as high intensity alveolitis [109] weakened as it was made obvious that even advanced cases may show a normal BAL lymphocyte count [113, 114]. BAL lymphocyte counts appear too unreliable as a single investigative tool to be of help regarding therapeutic decisions in patients receiving corticosteroid treatment [115].

A characteristic pattern of BAL macrophage phenotypes identified by monoclonal antibodies...
(BOOP), human immune deficiency virus (HIV) infected patients and drug induced pneumonitis.

It is worth mentioning that the presence of very high percentages of lymphocytes in association with increases in mast cells >1% might represent a diagnostic indicator of EAA [22]. Of course, this combination is only of value in cases which are currently, or have been recently, exposed to antigen since mast cells return to the normal range within one to three months after removal from exposure.

The pattern of alveolitis in EAA during the follow-up

Although it is difficult to precisely separate patients on the basis of antigen exposure and, thus, correctly subdivide EAA cases into strictly defined groups, a distinction needs to be made between patients who continue to be exposed to antigens and patients who had been removed from the antigenic exposure.

Concerning those patients who continue to be exposed to antigens, several authors have shown a decrease (percentage or absolute) of lymphocytes during the follow-up [137, 138] while other authors have demonstrated that the increase of the total number of lymphocytes was a persistent feature in EAA patients still exposed to relevant antigens [139]. With regard to immunological surface markers, a recovery of the CD4/CD8 ratio has been evidenced during the follow-up only in those patients who had been removed from further antigen exposure [138, 140], thus suggesting that the immunological abnormalities in these patients progress towards normal. Note that the behaviour of the CD4/CD8 ratio is not consistent in all cases. A recovery of the CD4/CD8 ratio was not found in subjects still exposed to relevant antigens [141].

As far as clinical management is concerned, studies performed on this topic have indicated that there is no correlation between radiographic changes, pulmonary function, BAL findings or levels of precipitating antibodies and different phases of the disease [141-144].

Analysis of humoral constituents of BAL

The analysis of humoral constituents of BAL does not significantly improve the diagnosis of patients with EAA, as compared to the great value of the BAL cytology and immunocytology in the clinical assessment of this disease. However, the evaluation of hyaluronate and type III procollagen peptide concentrations in BAL might be useful in monitoring the disease [60, 145].

Table 1. – Evolution of alveolitis in patients with extrinsic allergic alveolitis

<table>
<thead>
<tr>
<th>Time from acute episode</th>
<th>Type of reaction</th>
<th>BAL findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>4-72 h</td>
<td>mediated by immune complexes</td>
<td>increase of neutrophils, mast cells, plasma cells</td>
</tr>
<tr>
<td>3rd day to weeks</td>
<td>mediated by suppressor/ cytotoxic lymphocytes</td>
<td>increase of CD8+ cells</td>
</tr>
<tr>
<td>Several months</td>
<td>delayed type hypersensitivity</td>
<td>increase of CD8+ cells, CD4+ cells</td>
</tr>
</tbody>
</table>

Occupational lung diseases due to inhalation of inorganic dust


This chapter aims to review the clinical use of BAL in patients with interstitial lung disease (ILD) associated with occupational or environmental exposure to inorganic dust and minerals. Excluded from this paper are occupational asthma and ILD due to inhalation of organic dusts (extrinsic allergic alveolitis).

Indications for performing a BAL in ILD associated with inorganic dust exposure are: 1) the exclusion of other causes of ILD, such as sarcoidosis, pulmonary haemorrhage syndromes, malignancies etc., in patients additionally exposed to inorganic dust; 2) the documentation of mineral dust exposure in patients who may not be aware of being at increased risk of dust inhalation; 3) the documentation of the local immune and inflammatory reaction, i.e. the alveolitis.
Table 1. – How many subjects show signs of alveolitis

<table>
<thead>
<tr>
<th>Authors</th>
<th>[Ref.]</th>
<th>Type</th>
<th>Increased lymphocytes</th>
<th>Increased neutrophils</th>
</tr>
</thead>
<tbody>
<tr>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>Gellert</td>
<td>[35]</td>
<td>1985</td>
<td>ASB</td>
<td>8/27 (29%)</td>
</tr>
<tr>
<td>Xaubet</td>
<td>[158]</td>
<td>1986</td>
<td>EXP</td>
<td>0/15 (0%)</td>
</tr>
<tr>
<td>Robinson</td>
<td>[154]</td>
<td>1986</td>
<td>ASB</td>
<td>0/27 (0%)</td>
</tr>
<tr>
<td>Rom</td>
<td>[151]</td>
<td>1987</td>
<td>ASB</td>
<td>3/27 (11%)</td>
</tr>
<tr>
<td>Haslam</td>
<td>[159]</td>
<td>1987</td>
<td>ASB</td>
<td>3/27 (11%)</td>
</tr>
<tr>
<td>Costabel</td>
<td>[146]</td>
<td>1990</td>
<td>EXP</td>
<td>10/29 (34%)</td>
</tr>
<tr>
<td>---</td>
<td>---</td>
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</table>

Silicotic disease (SIL) and exposure (EXP)

<table>
<thead>
<tr>
<th>Author</th>
<th>[Ref.]</th>
<th>Type</th>
<th>Increased lymphocytes</th>
<th>Increased neutrophils</th>
</tr>
</thead>
<tbody>
<tr>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>Gellert</td>
<td>[35]</td>
<td>1985</td>
<td>SIL-EXP</td>
<td>16±4 (56%)</td>
</tr>
<tr>
<td>Xaubet</td>
<td>[158]</td>
<td>1986</td>
<td>EXP</td>
<td>normal</td>
</tr>
<tr>
<td>Robinson</td>
<td>[154]</td>
<td>1986</td>
<td>ASB</td>
<td>normal</td>
</tr>
<tr>
<td>Spurzem</td>
<td>[156]</td>
<td>1987</td>
<td>EXP+ASB</td>
<td>30±5</td>
</tr>
<tr>
<td>Rom</td>
<td>[151]</td>
<td>1987</td>
<td>ASB</td>
<td>21±4</td>
</tr>
<tr>
<td>Haslam</td>
<td>[159]</td>
<td>1987</td>
<td>ASB</td>
<td>normal</td>
</tr>
<tr>
<td>Wallace</td>
<td>[148]</td>
<td>1989</td>
<td>EXP</td>
<td>19±3</td>
</tr>
<tr>
<td>Costabel</td>
<td>[146]</td>
<td>1990</td>
<td>EXP</td>
<td>17±4</td>
</tr>
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<td>---</td>
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</tr>
</tbody>
</table>

Table 2. – Mean values of BAL cell differentials

<table>
<thead>
<tr>
<th>Author</th>
<th>[Ref.]</th>
<th>Type</th>
<th>Increased lymphocytes</th>
<th>Increased neutrophils</th>
</tr>
</thead>
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<tr>
<td>---</td>
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</tr>
<tr>
<td>Gellert</td>
<td>[35]</td>
<td>1985</td>
<td>ASB</td>
<td>11%</td>
</tr>
<tr>
<td>Xaubet*</td>
<td>[158]</td>
<td>1986</td>
<td>EXP</td>
<td>normal</td>
</tr>
<tr>
<td>Robinson</td>
<td>[154]</td>
<td>1986</td>
<td>ASB</td>
<td>normal</td>
</tr>
<tr>
<td>Spurzem</td>
<td>[156]</td>
<td>1987</td>
<td>EXP+ASB</td>
<td>30±5</td>
</tr>
<tr>
<td>Rom</td>
<td>[151]</td>
<td>1987</td>
<td>ASB</td>
<td>21±4</td>
</tr>
<tr>
<td>Haslam</td>
<td>[159]</td>
<td>1987</td>
<td>ASB</td>
<td>normal</td>
</tr>
<tr>
<td>Wallace</td>
<td>[148]</td>
<td>1989</td>
<td>EXP</td>
<td>19±3</td>
</tr>
<tr>
<td>Costabel</td>
<td>[146]</td>
<td>1990</td>
<td>EXP</td>
<td>17±4</td>
</tr>
<tr>
<td>---</td>
<td>---</td>
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</table>

Silicotic disease (DIS) and exposure (EXP)

<table>
<thead>
<tr>
<th>Author</th>
<th>[Ref.]</th>
<th>Type</th>
<th>Increased lymphocytes</th>
<th>Increased neutrophils</th>
</tr>
</thead>
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<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
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</tr>
<tr>
<td>Gellert</td>
<td>[49]</td>
<td>1985</td>
<td>SIL-EXP</td>
<td>16±4 (56%)</td>
</tr>
<tr>
<td>Xaubet</td>
<td>[158]</td>
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<td>EXP</td>
<td>normal</td>
</tr>
<tr>
<td>Robinson</td>
<td>[154]</td>
<td>1986</td>
<td>ASB</td>
<td>normal</td>
</tr>
<tr>
<td>Spurzem</td>
<td>[156]</td>
<td>1987</td>
<td>EXP+ASB</td>
<td>30±5</td>
</tr>
<tr>
<td>Rom</td>
<td>[151]</td>
<td>1987</td>
<td>ASB</td>
<td>21±4</td>
</tr>
<tr>
<td>Haslam</td>
<td>[159]</td>
<td>1987</td>
<td>ASB</td>
<td>normal</td>
</tr>
<tr>
<td>Wallace</td>
<td>[148]</td>
<td>1989</td>
<td>EXP</td>
<td>19±3</td>
</tr>
<tr>
<td>Costabel</td>
<td>[146]</td>
<td>1990</td>
<td>EXP</td>
<td>17±4</td>
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</tbody>
</table>

*: data are mean±sD; SIL: silicosis; CWP: coal workers’ pneumoconiosis; MDP: mixed dust pneumoconiosis.

**Table 2.** – Mean values of BAL cell differentials

**Inflammatory cell profiles**

The total number of cells recovered is either normal [49, 146–148] or slightly increased [149–152]. As in other types of ILD it is important to correct the total cell count for smoking habits [153].

BAL findings

Usually, the severity of the alveolitis in patients with occupational dust exposure is mild in intensity. Many patients show a normal BAL cell profile (table 1). In those patients who have a relative increase in lymphocytes and/or neutrophils, the increase is moderate when looking at the mean of values of different study groups so far reported in the literature (table 2), except for those with chronic beryllium disease.
The type of alveolitis, whether associated with a lymphocytic or a neutrophilic/eosinophilic predominance, or with an increase in both, is summarized in Table 2. In patients with lone increase in neutrophils caution must be taken regarding the diagnostic interpretation, since moderate increases can arise in chronic bronchitis, in particular in smokers, which has a high incidence in this population.

Asbestos disorders. In subjects with known exposure to asbestos, but without radiographic or functional signs of ILD, the most frequent finding is a lymphocytic alveolitis. In fact, in this group of subjects, the mean values of BAL lymphocytes, range between 17-30% [146, 148, 155, 156] and are usually higher than in patients suffering from confirmed asbestos. See Table 2.

In patients with asbestosis, the data in the literature about a neutrophilic alveolitis are more conflicting, since the mean values reported so far vary considerably, see table 2 [35, 146, 151, 154, 157-159].

Different forms of occupational exposure and different types of asbestos fibres may explain these discrepancies, and future studies should address this topic.

Silicotic disorders. In the silicotic group of patients, data in the literature seem to be more consistent. In coal workers pneumoconiosis a normal percentage of lymphocytes and a mild increase in neutrophils has been reported [151, 152]. In other forms of silica exposure or disease, mainly mixed dust pneumoconiosis, a moderate increase in lymphocytes, sometimes also in neutrophils, has been described [49, 146, 147, 149-151].

Hard metal lung disease. In hard metal lung disease also, the percentage of lymphocytes may be mildly increased [160, 161]. Others have reported an increase in neutrophils and/or eosinophils [162, 163]. An additional characteristic feature of this disease is the presence of increased numbers of giant cells in BAL fluid [162, 163].

Chronic beryllium disease. Chronic beryllium disease is a granulomatous lung disorder that is histologically and clinically identical to sarcoidosis. The BAL cytology shows the same profile as active sarcoidosis with a marked increase in lymphocytes that bear the phenotype of activated T-helper cells namely the CD4+HLA-DR+ phenotype [164-167].

The main difference to sarcoidosis is that the antigen is known in chronic beryllium disease. This fact can be used for a specific diagnostic in vitro test measuring the proliferative response to beryllium salts of blood or BAL lymphocytes. In this lymphocyte transformation test, the specific response is almost entirely confined to the CD4+ T-cell subset [167], and is significantly greater from BAL than from blood cells [164, 166, 168]. The blood cell response does not clearly separate patients with chronic beryllium disease from normal controls or from patients with sarcoidosis, whereas with BAL cells the sensitivity of this test has been reported to be 100% in 14 patients with definite chronic beryllium disease, and also the specificity was found to be 100%, indicating that chronic beryllium disease can specifically be diagnosed by a positive proliferative response of BAL cells to beryllium salts [145].

Lymphocyte subpopulations

For asbestosis or asbestos exposure, several groups confirmed that the CD4/CD8 ratio is elevated in some individuals [146, 148, 160, 169, 170]. Only one group reported a decrease in the CD4/CD8 ratio in asbestosis [157]. There are reports indicating that the CD4/CD8 ratio is greater in those with pleural plaques [148, 170]. This relationship was not found in another study, however [146]. The most marked increase in the CD4/CD8 ratio occurs in chronic beryllium disease [166]. A decrease in the CD4/CD8 ratio has been described in silicotic disease [146, 147, 149, 169] and in hard metal lung disease [160, 161].

Detection and quantification of dust particles and fibres

The different methods for identification of particles and fibres in BAL have been extensively reviewed in the previous report of this task group on the technical aspects of BAL [1]. The detection of particles characteristic enough for a certain exposure is already possible by routine light microscopy screening. The formation of ferruginous bodies occurs after inhalation of dusts of various kinds. Most frequently such bodies present true asbestos bodies when they are regularly shaped and regularly segmented with a fine central fibre almost invisible by the light microscope [171]. Other fibres that are thicker or irregularly shaped lead to the formation of pseudo-ferruginous bodies, including talc, glass fibres, and coal dust particles [172, 173].

The presence of dust particles in the cytoplasm of alveolar macrophages may suggest exposure to crystalline and metallic particles including silica [49], coal dust, hard metal [162, 172], antimony [174], aluminium [175], iron-rich particles, and alloys used in dentistry [176].

The exact analysis of the chemical composition of the particles can be done by electron microscopy making use of energy dispersive X-ray analysis (EDAX). From this, conclusions regarding the mineral composition of the particles can be drawn [49, 172, 177]. Quantification of the alveolar dust burden has been performed by EDAX microanalysis in silica exposed subjects and shown to be significantly higher than in unexposed controls, but there was no difference between subjects with silicosis and those with exposure only and no disease, regarding the total amount of silica in the BAL samples [178]. Another method is the neutron
The clinical role of BAL in pulmonary histiocytosis X

C. Danel, D. Israel-Biet, U. Costabel, G.A. Rossi, B. Wallaert

Pulmonary histiocytosis X (PHX) is a rare chronic granulomatous disorder involving cells of the mononuclear system. The diagnostic feature of this disease is the finding of Langerhans cells (LC) which react with the monoclonal antibody CD1 (OKT6) and which contain characteristic cytoplasmic organelles [183, 184]. After its introduction as a new means of studying peripheral lung and alveolar cell populations, BAL has rapidly proved useful in the diagnosis of PHX [185].

Diagnostic value of BAL in PHX

Several studies have shown the major value of BAL in the diagnosis of PHX [185, 186]. The total cell count is usually increased. HANCE et al. have reported that 90% of their PHX patients were smokers [186]. It is well known that the total cell recovery is usually higher in smokers than in nonsmokers. Besides, the nonsmoking patients with PHX have a normal alveolar cell count. The differential cell count shows a high percentage of alveolar macrophages (AM), a slight increase of neutrophils and eosinophils [185]. On electron microscopy, a significant percentage of Langerhans cells (LC) display highly specific pentalaminar structures of constant width, with a tennis racket shape at one end [183, 185]. As this ultrastructural analysis is time consuming, a more rapid and sensitive technique has been developed using monoclonal antibodies to LC (CD1 positive cells) [184]. For some other authors, the finding of PS 100 BAL positive cells could ensure the diagnosis of PHX. However, this antibody is far less specific of LC than CD1 and its use is therefore not recommended.

The actual value of BAL and in particular the presence of LC in the diagnosis of PHX is difficult to assess. Some authors have reported a mean of 5% CD1 positive cells in the BAL of patients with PHX, while in other interstitial lung diseases, less than 3% of the total cells were found to be CD1 positive [184]. In fact, recent studies have shown that LC are normally present in the lower respiratory tract and in lung parenchyma of normal subjects, particularly in smokers [186, 187]. Alteration of this epithelium seems to an important stimulus in attracting LC to the lung [130], and cigarette smoking is known to produce such epithelial abnormalities in the lower respiratory tract. Besides, cigarette smoke actually increases the number of LC found in BAL fluid [186]. Furthermore, LC have been found in the lung of patients with diseases other than PHX, in fibrotic lung disorders, benign inflammatory conditions or bronchoalveolar carcinoma for instance [65, 167, 168]. Therefore, as the mere presence of LC in BAL is not pathognomonic of PHX, particularly in smoking patients, a percentage of at least 5% of CD1 labelled alveolar cells is required to confirm the diagnosis.
On the other hand, with PHX having a patchy distribution, a localized BAL can miss the diagnosis, as well as a transbronchial biopsy. Confirmation by an open lung biopsy is therefore advisable.

Conclusions

There are strong arguments to support the usefulness of lavage cell analysis in the diagnosis of pulmonary eosinophilic infiltrates in the lung can be encountered in a great variety of disorders such as asthma, eosinophilic pneumonia, allergic bronchopulmonary aspergillosis or Churg and Strauss vasculitis. In this chapter we will concentrate on eosinophilic pneumonia ranging from the acute but mild and remitting Loeffler's syndrome to the severe chronic eosinophilic pneumonia. As these diseases can be life-threatening but remarkably reversible under corticosteroid therapy, a rapid diagnosis is of major importance. Since no alveolar eosinophilia is ever observed in normal controls, any increase in the percentage of eosinophils in BAL argues for a pathological process. In any type of eosinophilic lung (EL), acute or chronic, BAL always displays a high alveolar eosinophilia, whether or not associated with a blood eosinophilia [190–193].

Besides its diagnostic value, BAL has also given clues to the pathogenesis of eosinophilic lung injury. Indeed, eosinophils secrete not only neutral proteases and oxygen radicals but also a major basic protein (MBP) and a cationic protein (ECP) known to be able to induce acute lung damage and pulmonary fibrosis [194]. Finally, BAL is also valuable in EL for the clinical follow-up of patients under treatment [195].

Diagnostic value of BAL in eosinophilic lung

As, in these disorders, eosinophils are largely located in air spaces, the diagnostic yield of BAL is very high, usually making more invasive techniques (open lung biopsy or transbronchial biopsy) unnecessary. The analysis of BAL and blood should be performed in parallel. The diagnostic value of a high alveolar eosinophilia is all the greater if the level of the blood eosinophilia is normal.

It is usually in eosinophilic pneumonia (EP) that the highest eosinophilic count is observed [190–193]. If the increase of total recovered cells is not always significant, the percentage of eosinophils is markedly abnormal, sometimes increased up to 90% of total cells, associated or not to a few mast cells, and always higher than the neutrophil count. A proportion of these eosinophils can undergo necrosis, and fine eosinophilic granules can be observed in alveolar macrophages. Nevertheless, such a high alveolar eosinophilia can also be observed in some parasitic disorders or in the Churg-Strauss syndrome [192]. Less pronounced eosinophil increases (5–10%) can be found in sarcoidosis, histiocytosis X, drug induced pneumonia, collagen vascular disease, asthma and idiopathic pulmonary fibrosis [190–192].

Conclusions

In eosinophilic lung diseases (EL), BAL is of great value not only for the diagnosis and the follow-up of patients treated, but also for the study of their pathogenesis. EL is one of the diseases in which BAL can give enough clues to the diagnosis to avoid, in many cases, an open lung biopsy. The highest eosinophil counts ever seen in BAL fluid are observed here, ranging from 20–90% of the cells. These results are most useful when the X-ray findings are atypical and peripheral eosinophilia absent.

The clinical role of BAL in alveolar proteinosis

C. Danel, D. Israel-Biet, U. Costabel, G.A. Rossi, B. Wallaert

Pulmonary alveolar proteinosis (PAP) is a rare disorder characterized by accumulation of periodic-acid-Schiff (PAS)-positive phospholipidic material in the alveolar spaces [196]. PAP can be idiopathic or secondary to various conditions, such as immunosuppression, malignant haematological disorders, silicosis or, more rarely, diffuse interstitial lung diseases [53, 196, 197].

As the clinical and radiological presentations are not specific, PAP can remain misdiagnosed. Segmental BAL appears to be essential in management of this disease for diagnosis, follow-up, and therapeutic purposes [197].
**Diagnostic value of BAL in PAP**

Several studies have shown the major value of BAL in the diagnosis of PAP [196–198].

On gross examination, the BAL fluid has a milky appearance. After gravity sedimentation a dense tan sediment can also be observed. On light microscopy, the analysis of recovered cells shows an increase in total cell count [199–1009] probably partially explained by the fact that, in these studies, the majority of patients were smokers. On cytocentrifuged slides stained by MGG, the striking feature is the finding of a variable amount of basophilic extracellular deposit mixed with enlarged foamy alveolar macrophages (AM), crystal clefs and cellular debris. This extracellular material as well as the cytoplasmic content of the AM show a pink PAS positive diastase resistant staining. It should be noted that this staining is weaker than that observed in transbronchial biopsy (TBB) or open lung biopsy due to the dilution induced by the BAL fluid.

On electron microscopy the ultrastructural appearance is characteristic, with small lamellar bodies of wavy or regular periodicity, tubular myelin structures and myelin-like multilamellated structures with electron dense central region [101–102]. Added to this extracellular material, ghost cells, AM and/or pneumocytes II are filled with intracellular bodies and empty vacuoles or grey lipid droplets.

Different cellular profiles have been described. Some authors found an increase of lymphocytes compared to a control group with similar smoking habits [200] with an increased ratio of helper to suppressor T-cells. Others found a slight increase in neutrophils [203]. Particularly in these latter cases, a careful search for pathogens has to be undertaken.

In order to differentiate primary from secondary PAP, some authors have proposed an analysis of the alveolar material with specific antibodies against surfactant apoproteins. They have shown a significant difference in the quantity and repartition of the staining between primary and secondary forms [204].

Biochemical analysis of the lavage fluid, in particular protein and lipid analysis, have been performed by many laboratories. In comparison with normal subjects, a higher protein and phospholipid concentration is always present, and qualitative abnormalities in phospholipid composition have been found [53, 205]. Some authors have shown an impairment in AM function [199, 206].

**The value of BAL in comparison to other diagnostic procedures in PAP**

Few papers have compared the advantages of the different diagnostic procedures in PAP. However, in comparison with sputum analysis, transbronchial biopsy (TBB) or open lung biopsy, they have emphasized the major value of BAL [196, 197, 201, 202]. This is mainly due to the fact that PAP is an intra-alveolar disease and that, for instance, segmental BAL covers a larger distal lung field than TBB, the latter being sometimes equivocal if the disease is patchy. Nevertheless, the combination of both procedures will assure proper diagnosis. However, as TBB can induce alveolar space oedema and focal haemorrhages, BAL should be performed first.

The value of BAL in the follow-up and treatment of PAP is reported in the chapter dealing with therapeutic applications

**Conclusions**

Compared with other pulmonary disorders, PAP is certainly that in which BAL has a very high diagnostic yield, making open lung biopsy in most cases unnecessary. Furthermore, BAL is also of major value in the follow-up and the therapeutic management of patients with PAP.

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**The clinical role of BAL in pulmonary haemorrhages**

C. Danel, D. Israel-Biet, U. Costabel, G.A. Rossi, B. Wallaert

Many different clinical syndromes are included under the general heading of pulmonary haemorrhages (PH) and haemosiderosis (table 1). The triad of haemoptysis, infiltrates on chest X-ray and anaemia are present in most of the cases, however active PH does occur without these findings.

Furthermore, a delay in diagnosing PH can lead to fatal renal or pulmonary complications. Therefore, a rapid diagnosis is important and BAL appears to be the method of choice especially to diagnose distal occult PH and to eliminate other underlying diseases such as infections or malignancies.

---

**Diagnostic value of BAL in pulmonary haemorrhages**

On gross examination, the BAL fluid has either a bloody or orange-pink colour, or can be of normal translucent appearance.

On light microscopy, compared with nonsmoking controls, the total cellular count and the percentage of AM are increased [207]. Several morphological aspects can be observed such as free red blood cells, red blood cells in alveolar macrophages (AM) and haemosiderin laden AM. The importance of the haemosiderin content can be evaluated either by the percentage of AM...
Table I - Principal disorders associated with diffuse pulmonary haemorrhage (PH) and haemosiderosis

1. PH secondary to cardiac disease, intrapulmonary vascular lesions or malformations.
   - Chronic left- or right-sided heart failure (mitral stenosis).
   - Pulmonary hypertension.
   - Pulmonary veno-occlusive disease.
   - Pulmonary lymphangiomatosis.
   - Arteriovenous fistulas or other congenital vascular malformations.
   - Vascular thrombosis with infarction.

2. Pulmonary haemosiderosis and glomerulonephritis.
   - With anti-basement membrane antibody (ABMA) disease.
   - Without ABMA.
   - With immune complex-mediated.

3. Idiopathic pulmonary haemosiderosis.

4. PH associated with vasculitides and collagen vascular disease.
   - Systemic lupus erythematosus.
   - Wegener granulomatosis.
   - Mixed connective tissue disease.
   - Idiopathic thrombocytopenic purpura.

5. PH associated with miscellaneous disorders.
   - Diffuse necrotizing infections.
   - Severe coagulopathy.
   - Malignant diseases such as acute leukaemia.

6. PH associated with drugs.
   - D-penicillamine.
   - Amphotericin B
   - Chemotherapy drugs

    containing haemosiderin or by a score proposed by Golde and co-workers [208, 209]. This haemosiderin score (HS) is based on the colour intensity of AM cytoplasm on an iron stain (i.e. Prussian blue).

    The presence of intact red blood cells in the lavage fluid is not in itself a definite sign in favour of AH, it can be related simply to minor trauma during the bronchoscopy. However, in acute PH such as in Goodpasture’s syndrome, BAL can be bloody without haemosiderin laden AM [210]. In fact, rather than a bloody BAL fluid, free red blood cells or red blood cells in AM, it is the presence of numerous haemosiderin laden macrophages, appearing at least 48 h after bleeding, which strongly suggests pulmonary haemorrhage [211]. When one observes not only a large increase in the percentage of AM containing haemosiderin deposits, but also an increase in the intensity of the haemosiderin content (HS >100), the diagnosis of alveolar haemorrhage can be confirmed. In the evaluation of the bleeding, this HS appears more sensitive [207, 212]. In fact, in many pulmonary disorders without significant bleeding, light haemosiderin deposits can be observed, even in a large percentage of AM (such as in immunosuppressed patients).

Comparison of BAL and other diagnostic procedures in PH

Few papers have compared the advantage of the different diagnostic procedures in AH. Compared with transbronchial biopsy (TBB) or open lung biopsy, they have mostly emphasized that BAL is a less invasive technique, particularly important in patients with low platelet counts or bleeding disorders, where biopsy may often be impossible because of the high risk of bleeding [207, 208].

Some authors [207, 212] have compared the haemosiderin score (HS) in BAL [208] and pulmonary parenchyma obtained by TBB, open lung biopsy and from post-mortem specimens. They have shown that in BAL HS was a very good marker of pulmonary haemorrhage. In particular, a high HS is always associated with histological evidence of severe pulmonary haemorrhage. Kahn et al. [207] conclude that an HS greater than 100 is indicative of severe pulmonary haemorrhage. On the contrary, there is no correlation between the bloody appearance of the BAL fluid or large number of red blood cells per mm³ and either an elevated HS or the presence of alveolar haemorrhage in tissue specimens.

Conclusions

BAL appears to be the method of choice to confirm pulmonary bleeding especially in occult alveolar haemorrhages and to search for an underlying disease such as infection or malignancies. It is a safe procedure with minimal and rare complications particularly in patients with low platelet counts or bleeding disorders and can be performed in virtually all cases regardless of the severity of the disease.

Drug induced pneumonitis

C. Danel, D. Israel-Biet, U. Costabel, G.A. Rossi, B. Wallaert

Since the list of drugs that may adversely affect the lung grows longer every day, the problem is not to be exhaustive in naming every one of them but to have reliable criteria by which to suspect and to recognize an iatrogenic lung disease early enough to prevent the development of irreversible injury [213, 214]. In this context, BAL has proved to be a very useful tool in the diagnostic approach. It can provide evidence to differentiate between iatrogenic causes, and to distinguish these from infectious or malignant aetiologies.
In table 1 are listed the main drugs known to be responsible for an iatrogenic lung injury. The pathogenic mechanisms are usually multifactorial.

Table 1. – Main drugs known to be responsible for iatrogenic lung injury

1. Drugs inducing pulmonary haemorrhages
   - D-penicillamine
   - Amphotericin B

2. Drugs inducing a lymphocytic/neutrophilic/eosinophilic alveolitis
<table>
<thead>
<tr>
<th>Lymphocytic</th>
<th>Neutrophilic</th>
<th>Eosinophilic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methotrexate</td>
<td>Bleomycin</td>
<td>Bleomycin</td>
</tr>
<tr>
<td>Azathioprine</td>
<td>Busulphan</td>
<td>Nitrofurantoin</td>
</tr>
<tr>
<td>Bleomycin</td>
<td></td>
<td>Cotrimoxazole</td>
</tr>
<tr>
<td>Busulphan</td>
<td></td>
<td>Penicillin</td>
</tr>
<tr>
<td>Nitrofurantoin</td>
<td></td>
<td>Salazopyrin</td>
</tr>
<tr>
<td>Acebutolol</td>
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<td></td>
</tr>
<tr>
<td>Gold salts</td>
<td></td>
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</tr>
<tr>
<td>Salazopyrin</td>
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<tr>
<td>Amiodarone</td>
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<tr>
<td>Propanolol</td>
<td></td>
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<tr>
<td>Diphenylhydantoin</td>
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</table>

3. Drugs inducing a thesaurismosis
   - Amiodarone
   - Potentially, all the amphiphilic drugs

Diagnostic value of BAL in drug induced lung diseases

In rare cases, BAL can be sufficient to confirm a suspected diagnosis. The best example is the exogenous lipid pneumonia induced by mineral oil, taken as nose drops or laxatives. In these cases, alveolar macrophages contain large empty vacuoles representing fatty material strongly stained by the oil red O. Chromatography on thin slices performed on the lipid extract of BAL shows the same physical profile as the drug involved [215].

In some cases of direct toxicity due to drugs such as bleomycin, cyclophosphamide and nitrofurantoin, various forms of pulmonary reactions can be observed, such as diffuse alveolar damage, eosinophilic pneumonia, or secondary alveolar proteinosis. In these cases, BAL will show atypical cells, a high percentage of eosinophils or extracellular lipoproteinaceous debris suggesting a diagnosis of drug induced toxicity.

More frequently, BAL has to be interpreted in the light of other diagnostic information (clinical history and examination findings, radiological features, etc.), the cytological profiles encountered here are few and non-specific. Schematically alveolar haemorrhages can be observed, mainly induced by D penicillamine. However, the most frequent BAL feature observed is an alveolitis characterized by an increase in total recovered cells among which one particular cell type can be markedly predominant (lymphocytic alveolitis) [216]. An increase of polymorphonuclear cells and morphological alterations of alveolar macrophages (thesaurismosis) can also be observed [217, 218]. The hyperlymphocytosis in the context of a drug induced pneumonitis can be as high as 80% of the recovered cells, but usually averages 40–50% [216, 217]. A predominance of suppressor/cytotoxic T-cells of the CD8 type with an inversion of the CD4/CD8 ratio is usually observed [216, 218]. Rarely a predominance of helper T-cells (CD4) is described, such as in methotrexate or nitrofurantoin induced pneumonitis [219, 220]. Associated with the CD8 lymphocytosis, a small proportion of eosinophils, mast cells and basophils is commonly found. Concurrently, although not routinely examined, the BAL fluid composition can be modified in particular with an increase in immunoglobulins [218]. All these features are similar to those found in classical hypersensitivity pneumonitis due to organic antigens. This underlines the fact that such environmental exposures must be excluded before confirming the iatrogenic origin of the lung disease.

An extremely high percentage of unaltered neutrophils usually argues for a very early stage (<48 h) of drug induced hypersensitivity, particularly if a concurrent alveolar haemorrhage is observed [217, 218]. In other cases the percentage of neutrophils averages 10–30%, suggesting the development of a pulmonary fibrosis. This can be due either to a neglected hypersensitivity or to the direct toxicity of drugs such as bleomycin.

Certain drugs, such as amiodarone or more generally any amphiphilic molecule can lead to thesaurismosis. In this disorder, ultrastructural studies of BAL show an accumulation of numerous large lamellar inclusions, phospholipidic in nature, mainly in alveolar macrophages, but also in neutrophils, lymphocytes and bronchial cells [218, 221]. These features have been observed in treated patients whether or not they have developed a pneumonitis. In contrast, hyperlymphocytosis associated with a thesaurismosis has been observed only in treated patients with pneumonitis [211]. Thus, it seems that thesaurismosis is necessary but not sufficient for the development of pneumonitis, which requires in addition an immune mechanism. In these cases BAL alone has no definite diagnostic value but becomes very suggestive in the context of an appropriate clinical presentation.

Conclusions

In drug induced pneumonitis, BAL can show different cellular profiles. None of them is absolutely specific and therefore BAL is not sufficient in itself to give a diagnosis. Nevertheless, it may help in eliminating alveolar haemorrhages, infectious disorders or the recurrence of an underlying disease such as malignancy, which could also be responsible for the pulmonary symptoms. Finally, besides the clinical value of BAL reported above, it should be stressed that it has given several clues to the pathogenic mechanisms of these disorders.
The clinical use of BAL in patients with pulmonary infections

M. Rust, C. Albera, L. Carratu, C. Danel, D. Israel-Biet, H. Klech, S.I. Rennard, A.J.A. Robalo-Cordeiro, G. Semenzato, G. Velluti, H. Worth

In immunocompetent patients with community acquired pneumonia, as well as in the immunocompetent host with nosocomial pneumonia, a calculated therapy can be initiated without prior invasive diagnostic procedure. This kind of patient management, however, is not warranted in immunocompromised or immunodeficient patients, in whom an exact diagnosis and the identification of the organism causing pneumonia is of utmost importance to select the correct therapeutic regime. If less invasive techniques like blood cultures were not successful in establishing the diagnosis, or the results from other procedures such as sputum induction were nondiagnostic, it is necessary to obtain specimens from the lower respiratory tract. These specimens can be taken using transtracheal aspiration, fiberoptic bronchoscopy, transthoracic needle puncture, or open lung biopsy. Such invasive procedures may also be necessary in the immunocompetent host, if therapy for a community acquired pneumonia or nosocomial pneumonia have failed and less invasive procedures are not likely to identify the cause of the disease.

As experience during the past years has shown, taking microbiological samples by protected brush, bronchoalveolar lavage and/or transbronchial lung biopsy are methods which combine a low rate of side-effects and a sufficient diagnostic yield when used in this context [222-224]. Also bronchoalveolar lavage alone is a sensitive method to establish the diagnosis of infection of the lower respiratory tract caused by bacteria [222, 223], mycobacteria [225], viruses [226] and other opportunistic infections of the lung (e.g. Pneumocystis carinii pneumonia) [227, 228] (summary in table 1).

### Table 1. - Microbiological diagnosis from BAL

<table>
<thead>
<tr>
<th>Technique, stains</th>
<th>Value</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>P. carinii</td>
<td>Wright-Giemsa, Diff Quick, Gomori-Grocott</td>
<td>80-90% sens.</td>
</tr>
<tr>
<td>Cytomegalovirus</td>
<td>Virus cell inclusions, Immunofluoresce, Immunochem. DNA probe analysis</td>
<td></td>
</tr>
<tr>
<td>Herpes simplex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mycobacteria</td>
<td>Ziehl-Neelsen, Auramin-Rhodamin</td>
<td>atyp, typ. Tbc</td>
</tr>
<tr>
<td>Fungi</td>
<td>Silverstain, Monoclonal antibod.</td>
<td>Candida, Aspergillus, Alternaria</td>
</tr>
<tr>
<td>Bacteria</td>
<td>Gram stain, Semiquant. counting of CFU</td>
<td>Colonization or infection</td>
</tr>
<tr>
<td>Legionella</td>
<td>Direct immunofluoresce.</td>
<td></td>
</tr>
</tbody>
</table>

### Indications for bronchoalveolar lavage in patients with pulmonary infections

Immunodeficient or immunocompromised patients. In the clinical setting of an immunocompromised host (e.g. patients receiving immunosuppressive agents) or immunodeficient host (e.g. neutropenic patients) having pulmonary infiltrates suggesting lower respiratory tract infection, we recommend use of bronchoalveolar lavage as a means of obtaining samples from the lower respiratory tract for microbiological work-up. If the platelet count is normal, no clotting abnormalities are present and the patient is not at risk for mechanical ventilation, a transbronchial lung biopsy may be performed at the same time. Although TLB is not recommended in patients with thrombopenia or clotting abnormalities, a normal BAL has been safely applied even in thrombocytopenic and granulocytopenic patients after intensive cytotoxic therapy in conjunction with bone marrow transplantation [229].

In patients with an advanced HIV infection and suspected Pneumocystis carinii pneumonia an induced sputum [221] should precede the bronchoalveolar lavage. If sputum is nondiagnostic, BAL should be performed as soon as possible. In the majority of patients with HIV infection and pulmonary infiltrates the diagnosis can be established by BAL without additional transbronchial lung biopsy. BAL is reported to have a diagnostic yield to identify PC-infection of over 90%, followed by TLB with 75% and brush biopsy of only 32% [211]. Thus, considering the potential bleeding risk of an HIV infected patient with diffuse pulmonary Kaposis sarcoma, transbronchial lung biopsy should only be performed,
if prior investigations including BAL were nondiagnostic.

**Immunocompetent patients.** Bronchoalveolar lavage has been successfully used in this clinical setting also, in particular in patients suggestive for nosocomial pneumonia by help of Gram stains and bacterial cultures; semiquantitative counting of bacteria helps to differentiate between colonization and infection [222, 224, 239, 239]. Legionella infections can be detected either by direct immunofluorescence technique [240] or by bacterial culture.

**Technique of bronchoalveolar lavage**

Bronchoalveolar lavage is performed during fibroptic bronchoscopy as described previously [1]. Although some local anaesthesia may be necessary to perform this procedure, the anaesthetic should not be instilled directly into the segment to be lavaged, as it may inhibit bacterial growth in the culture. Bronchoalveolar lavage should be performed in a segment which has been shown to be infiltrated on chest radiograph or from which purulent secretion is discharged during bronchoscopy. In adult patients a volume of 50–100 ml of saline should be used in this clinical setting. For the interpretation of laboratory results from BAL it may be helpful to obtain specimens from the oral cavity and hypopharynx at the time of the BAL. Supplemental oxygen should be given during the entire procedure and for at least 1 h after the bronchoscopy.

As immunocompromised patients with a pneumonia are at risk to develop respiratory failure, prior to BAL an arterial blood gas analysis should confirm that the patient is not at risk to develop respiratory distress during or after bronchoalveolar lavage. If arterial oxygen tension (Pao2) despite supplemental oxygen is <65 mmHg bronchoalveolar lavage should be performed with care, reducing the volume of saline to be instilled. As the Pao2 may drop substantially after bronchoalveolar lavage, adequate preparations have to be taken so that the patient can be intubated and ventilated if necessary. During the procedure vital signs, oxygen saturation and cardiac rhythm should be monitored continuously.

**Work-up of specimens obtained by bronchoalveolar lavage**

Specimens obtained from immunocompromised or immunodeficient patients should be processed as soon as possible, thus avoiding further contamination or missing such agents as anaerobic bacteria.

Bronchoalveolar lavage fluid should be worked up for bacterial, fungal, opportunistic and viral infections. In addition the specimens should be examined by a cytopathologist to exclude a malignancy. The techniques used for these purposes are described in the technical recommendations and guidelines for BAL. In summary BAL fluid should be stained and cultured quantitatively for bacteria [224] using appropriate media, stained and cultured for mycobacteria including mycobacteria other than *M. tuberculosis* (MOTT) and for fungi. *Pneumocystis carinii* infection should be ruled out by appropriate stains (Wright-Giemsa, silver stain, toluidine blue or monoclonal antibodies). Viral infections should be excluded using antibodies, viral cultures and DNA/RNA-probe analysis. If necessary electron microscopy enables a rapid differentiation of virus in bronchoalveolar lavage fluid.

In patients with HIV infection and diffuse pulmonary infiltrates a cell differential on a bronchoalveolar lavage slide may help to establish the diagnosis of lymphocytic interstitial pneumonia. Results from staining with appropriate antibodies and the demonstration of HIV in material from BAL may indicate the presence of nonspecific interstitial pneumonitis [242].

**Interpretation of laboratory results**

Results from BAL of immunocompromised or immunodeficient patients should be evaluated with care, considering the underlying disease, the history, the immunological status and the clinical features. In particular, the presence of cytomegalovirus (CMV) as shown by cultures or DNA-probe does not always indicate a clinically relevant infection. In case of detection of fungi or bacteria the clinician has to decide whether there is an infection, which should be treated, or a mere colonization. Quantitative cultures [224] may help to distinguish these two conditions.

**Conclusions**

BAL is the method of choice in diagnosis of opportunistic infections (bacteria, viruses, fungi, protozoa) of the lower respiratory tract in particular in immunodeficient or immunocompromised patients. Highest diagnostic yield is reported in the diagnosis of *P. carinii* pneumonia (>90%), which in many cases obviates the need of a lung biopsy. BAL can even be performed in patients with underlying respiratory insufficiency or in thrombocytopenic patients provided appropriate safety measures and selection of patients are undertaken. In patients with bacterial infections BAL may contribute to discrimination between bacterial colonization or true parenchymatous infection.
The major diagnostic techniques to obtain material for the diagnosis of cancer were, and remain direct forceps biopsy of bronchoscopically visible tumours and transbronchial biopsy for peripheral lesions. Nevertheless, BAL can obtain material which can permit the cytological diagnosis of cancer. The criteria for the cytological diagnosis of cancer in the lung are well established [243]. However, since BAL is often performed and interpreted by pulmonologists [190] who are not trained cytologists and because the stains most often used by pulmonologists do not always reveal cytological detail, it is likely that the power of BAL to aid in the diagnosis of lung cancer has been underappreciated.

Table 1. – Examples of BAL used in the diagnosis of cancer

<table>
<thead>
<tr>
<th>Type of cancer</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary lung</td>
<td></td>
</tr>
<tr>
<td>Squamous</td>
<td>[229, 244–248]</td>
</tr>
<tr>
<td>Adenocarcinoma</td>
<td>[229, 244–247]</td>
</tr>
<tr>
<td>Large cell</td>
<td>[229, 244, 246, 247]</td>
</tr>
<tr>
<td>Small cell</td>
<td>[229, 244–246]</td>
</tr>
<tr>
<td>Bronchoalveolar</td>
<td>[249–251]</td>
</tr>
<tr>
<td>Metastatic</td>
<td></td>
</tr>
<tr>
<td>Solid tumours</td>
<td>[229]</td>
</tr>
<tr>
<td>Breast</td>
<td>[252]</td>
</tr>
<tr>
<td>Lymphangitic spread</td>
<td>[253, 254]</td>
</tr>
<tr>
<td>Haematological malignancy</td>
<td></td>
</tr>
<tr>
<td>Hodgkin’s</td>
<td>[255–257]</td>
</tr>
<tr>
<td>Non Hodgkin’s lymphoma</td>
<td>[251, 256, 258, 259]</td>
</tr>
<tr>
<td>Leukaemia</td>
<td>[74, 229, 256]</td>
</tr>
<tr>
<td>Waldenstrom’s</td>
<td>[260]</td>
</tr>
<tr>
<td>Myeloma</td>
<td>[256]</td>
</tr>
<tr>
<td>Mycosis fungoides</td>
<td>[261]</td>
</tr>
</tbody>
</table>

Table 2. – Diagnostic yield of bronchoalveolar lavage in lung cancer

<table>
<thead>
<tr>
<th>Contributor</th>
<th>[Ref.]</th>
<th>No. of cases</th>
<th>No. with both BAL and diagnosis of cancer</th>
<th>No. of cases positive by BAL</th>
<th>% of cases positive by BAL</th>
</tr>
</thead>
<tbody>
<tr>
<td>STRZ*</td>
<td></td>
<td>471</td>
<td>430</td>
<td>225</td>
<td>52</td>
</tr>
<tr>
<td>WORTH*</td>
<td></td>
<td>146</td>
<td>99</td>
<td>37</td>
<td>37</td>
</tr>
<tr>
<td>BAGLIN</td>
<td>[262]</td>
<td>46</td>
<td>21</td>
<td>13</td>
<td>62</td>
</tr>
<tr>
<td>PROZYSKNI*</td>
<td></td>
<td>124</td>
<td>124</td>
<td>44</td>
<td>35</td>
</tr>
<tr>
<td>LINDER</td>
<td>[229]</td>
<td>421</td>
<td>35</td>
<td>24</td>
<td>69</td>
</tr>
<tr>
<td>SCHABERG</td>
<td>[247]</td>
<td>31</td>
<td>21</td>
<td>3</td>
<td>14</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>730</td>
<td>346</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

For sites mean = 45
For cases mean = 47

*: unpublished results
Table 3. – Diagnostic yield for BAL in lung cancer

<table>
<thead>
<tr>
<th>Cell type</th>
<th>% Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bronchoalveolar cell carcinoma</td>
<td>92</td>
</tr>
<tr>
<td>Small cell</td>
<td>32</td>
</tr>
<tr>
<td>Squamous</td>
<td>27</td>
</tr>
<tr>
<td>Adenocarcinoma</td>
<td>66</td>
</tr>
<tr>
<td>Large cell</td>
<td>25</td>
</tr>
</tbody>
</table>

Data are reported for the various series available expressed as number of cases positive by BAL/number of cases of proven cancer undergoing BAL.

Table 4. – Methods for the diagnosis of malignancy by bronchoalveolar lavage

<table>
<thead>
<tr>
<th>Lavage technique: Lavage affected segment (CT may be helpful)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Options*: “bronchial” and “alveolar” specimens for separate processing volume prior to/after brushings and biopsies</td>
</tr>
<tr>
<td>Sample processing options*: Smears, Cytocentrifuge preparations, Membrane filter preparations, Cell pellets embedded in paraffin</td>
</tr>
<tr>
<td>Stains: Routine*: Papanicolaou, Wright-Giemsa, Haematoxylin and eosin</td>
</tr>
<tr>
<td>Special: Monoclonal antibodies for tumour markers</td>
</tr>
</tbody>
</table>

*: the “best” choice is undetermined; CT: computerized tomography.

A second limitation of lavage is that the cytological diagnosis of malignancy does not always correspond to the histologic pattern [253]. Thus, in the series of Linder, cytology agreed with biopsy in only 80% of cases. The major difficulty was in distinguishing large cell undifferentiated carcinoma from adenocarcinoma. A similar problem occurs with the severe dysplastic changes that can develop in airway epithelial cells in a variety of clinical circumstances including pneumonia, viral infections and following chemotherapy. These severe dysplastic changes can be very difficult to distinguish from malignant changes. These limitations of cytological methods must be considered when bronchoalveolar lavage is used in the diagnosis of lung cancer.

Several contributors to the current report have performed large series of bronchoalveolar lavage and have made a diagnosis of malignancy only very rarely. This has contributed to the impression that BAL has limited use in the diagnosis of cancer.

There are several reasons which may explain the low diagnostic yield at these centres: 1) case selection may have been very different at different centres; 2) pulmonologists interested in performing bronchoalveolar lavage for specific research goals may not have processed lavage specimens in a manner to maximize yield for malignancy. Some investigators, for example, throw away the first aliquot returned, which is relatively enriched for bronchial material. For malignancies originating in the bronchial tree, this may represent the material with the highest diagnostic yield. In addition, many investigators filter the fluid through loose-weave gauze in order to remove mucus. Malignant cells are often present as clumps and may be removed by such filtration procedures. Finally, many investigators have performed the procedure in patients with malignancy in order to investigate immunological abnormalities in these patients. They have intentionally lavaged sites not affected by the cancer. Thus, the relatively low diagnostic yield found by many investigators who have performed lavage for reasons other than to obtain diagnostic material, may reflect the interests of specific investigators rather than the utility of lavage to obtain material diagnostic of malignancy.

A number of tumour markers have been studied in bronchoalveolar lavage [246, 263]. While there is considerable interest among investigators in such markers, none has proved to be diagnostic. Thus, the use of these markers must be considered a research tool at present. Whether these markers will be helpful in following patients on a therapeutic protocol for malignancy is an interesting, but as yet unresolved, question. One investigator has suggested that cytological assessment of malignancy can be used for a similar purpose. Again, this must be considered a research undertaking. However, inasmuch as bronchoalveolar lavage might provide a means to assess efficacy of novel therapeutic strategies in lung cancer, it may become an important adjunct in clinical studies.

There is also a considerable interest in studying abnormalities in the patient with cancer. As such, a number of studies of bronchoalveolar lavage parameters have been undertaken in these patients. While these studies promise to provide some information as to why certain individuals develop malignancy and, perhaps, why these patients have increased incidences of lower respiratory tract infections, these studies are research studies.

It is difficult to summarize current consensus regarding the use of bronchoalveolar lavage for the diagnosis of lung cancer. Current practices vary from never performing this procedure for this indication to routinely performing this procedure for this indication. At institutions where this procedure is never performed, there is, obviously, no diagnostic yield associated with bronchoalveolar lavage. Centres where bronchoalveolar lavage has been found to be useful in the diagnosis of lung cancer are those where the procedure can be performed readily, the samples can be processed easily and trained personnel are available for the routine analysis of the specimens. In such a favourable setting, it would seem reasonable to include bronchoalveolar lavage in the diagnostic routine used to evaluate patients for lung cancer. This is particularly so considering that the procedure has exceedingly low morbidity, and the increased cost over performing a bronchoscopy with other diagnostic procedures is relatively low.
Bronchial asthma

L.M. Fabbri, V. De Rose, Ph. Godard, G.A. Rossi

In the past few years fibroptic bronchoscopy and bronchoalveolar lavage fluid analysis have been extended to subjects with asthma and they are increasingly used to study airway cell profile and fluid components, as well as to study the characteristics of the harvested cells in vitro [198, 264, 265]. Initial studies were performed in stable asthmatics who were free of bronchospasm, and suggested that bronchoalveolar lavage could be safely performed as a research tool in carefully selected, asymptomatic asthmatic subjects. The guidelines provided by two international committees set up to evaluate the use of bronchoalveolar lavage and record its application, recognized and established the safety of the procedure in those selected patients [1, 266]. Many studies have been carried out without major complications on stable asthmatics before and after bronchoprovocation with allergens or occupational agents, and an international workshop on the use of bronchoalveolar lavage in asthma established the criteria to perform this procedure safely during the course of asthmatic responses to asthmogenic stimuli, as a research tool [266].

The general conclusion from the literature is that the bronchoalveolar lavage technique is safe in asthma, and that as long as reasonable guidelines are chosen for the selection of patients, the mortality is zero and the morbidity is very low. However, special care should be exercised in asthmatic patients with marked bronchial responsiveness, and supplemental oxygen delivery and electrocardiographic (ECG) monitoring is strongly advised in patients with severe underlying diseases or in any critical conditions [1, 198, 266]. Additional criteria are provided to select patients to undergo bronchoalveolar lavage following aerosol or local bronchoprovocation [266].

Clinical application of bronchoalveolar lavage in asthma

The analysis of cells, mediators, proteins and enzymes obtained from the alveolar spaces and the in vitro study of cells recovered from the respiratory tract can help to elucidate pathogenic mechanisms in asthma. In stable, mild asthmatics no distinctive cellular profile is diagnostic although eosinophils, neutrophils, epithelial cells, metachromatic cells and lymphocytes may be increased [198, 264, 265]. There seems to be no difference between the cellular profile of atopic and non-atopic stable asthmatics.

The major limitation of the standard technique of BAL is its intrinsic low sensitivity due to the fact that large volumes of fluid are instilled both in the airways and in the alveoli. To obtain true bronchial lavage by using lower volumes of fluid, new techniques have been recently developed to lavage isolated airway segments employing either a double balloon bronchoscope or a double balloon tipped catheter inserted through a double lumen bronchoscope (see following sections). This technique is extremely promising both because it is specific for the airways and because it already allowed the consistent recovery of cells and mediators before and after bronchoprovocation from the airways of asthmatic subjects, and some of the results seem to be specific for asthmatic airways [267–269].

The lack of specificity of bronchoalveolar lavage cell profile in asthma would discourage any clinical application of this procedure, especially since the diagnosis and monitoring of the activity of the disease seem to be accomplished effectively by using objective functional parameters, such as the measurement of airway responsiveness to nonspecific stimuli and the assessment of the spontaneous diurnal variability of airflow obstruction. Few patients with current active asthma have been evaluated. In most of the studies carried out in asthmatics the level of airway hyperresponsiveness, when it was measured, varied from mild to moderate, the subjects were defined as asymptomatic, and there was no attempt to evaluate the activity of the disease by using more than one functional parameter (i.e. the spontaneous variability of the airflow obstruction in addition to the level of nonspecific airway responsiveness). Thus, the results of bronchoalveolar lavage analysis in those patients may not be relevant to asthma but just to well-controlled asthmatics.

In formulating a reasonable position about the clinical use of bronchoalveolar lavage and its analysis in asthmatic subjects, one must acknowledge that it is still an experimental procedure, that needs further assessment and it must continue to be included as part of clinical research protocols. It may be proved to be clinically helpful in the evaluation of pulmonary infiltrates in asthmatics [264].

Bronchoalveolar lavage has also been considered for the therapy of status asthmaticus or life-threatening asthma attacks [198, 270]. The technique used for therapeutic lavages was not in fact bronchoalveolar lavage but just segmental washings, both because the procedure was not standardized and because the fluid was not analysed. Because of the limited experience and the lack of carefully designed clinical trials, the therapeutic segmental washings in patients with asthma must still be considered experimental in nature and performed in selected patients by well-trained physicians with an extensive experience in this field (see chapter: Therapeutic applications of BAL). One further promising application of bronchoalveolar lavage in asthma may be the assessment of the cellular response to antiasthma therapy [271, 272].
Conclusions

In agreement with the recent state-of-the-art paper and review articles, we believe that there is no indication at present for the use of bronchoalveolar lavage in clinical practice for the diagnosis, staging, monitoring or therapy of bronchial asthma. The only indication that may prove to be clinically helpful is the presence of pulmonary infiltrates in asthmatics, particularly for the diagnosis of allergic broncho-pulmonary aspergillosis.

**Chronic bronchitis and emphysema**

E. Pozzi, V. De Rose, S.I. Rennard, L.M. Fabbri

Despite the widespread use of bronchoalveolar lavage (BAL) in several lung diseases, only a few studies have evaluated its usefulness in patients with chronic bronchitis and/or emphysema.

**Bronchoalveolar lavage in the diagnosis of chronic bronchitis and emphysema**

Chronic bronchitis is defined by the presence of symptoms, and emphysema by the presence of pathological enlargements of airspace with destructive changes in the walls, thus bronchoalveolar lavage has no application in the definition of the diagnosis of either disease. In addition, there is no indication at present for the use of such a procedure in clinical work for staging or monitoring the course of chronic bronchitis and emphysema because of the lack of specificity of the findings from bronchoalveolar lavage fluid analysis. Due to various degrees of severity of obstruction great care should be taken when lavaging these patients (see chapter on Side-effects and Safety of BAL).

**Findings in bronchoalveolar lavage fluid from chronic bronchitis and emphysema**

Asthma, chronic bronchitis and emphysema are grouped under the terminology of chronic obstructive pulmonary disease (COPD). At present, very little is known about the biochemical and cellular changes that occur in BAL in each stage of chronic bronchitis and emphysema, and it can be summarized in the following points: with the exception of smokers who have been well characterized and who are likely to have small airways disease, there is little information about bronchoalveolar lavage findings in subjects with obstruction of the small airways (small airways disease) and in subjects with simple chronic bronchitis.

In patients with COPD the recovered fluid is reduced to 10–40% of that instilled [273–276] and the bronchoalveolar lavage fluid contains an increased number of neutrophils as well as bronchial lavage fluid [274–277]. Bronchoalveolar neutrophilia is not specific for COPD, since it is present in smokers without COPD, patients with cystic fibrosis, and in some interstitial lung diseases [101, 198]. In BAL from patients with emphysema and alpha,-PI, deficiency there is a severe neutrophilia (77.8%±18.4 of the differential count), suggesting high elastase burden in the alveolar lining fluid and reduced concentrations of alpha,-PI, whereas the concentration of alpha,-macroglobulin and antileucoproteases is normal [275].

**Use of bronchoalveolar lavage in the therapy of chronic bronchitis and emphysema**

At present, bronchial lavage has a limited role in the therapy of chronic bronchitis and emphysema. It may be used in some selected cases for removal of abundant secretions.

In the future it could provide a useful method of assessment of the effect of therapy. For example, according to the hypothesis that lung destruction in COPD is primarily mediated by a protease/antiprotease imbalance in the lower respiratory tract, the prevention of structural changes leading to severe functional impairment might be obtained by enhancing the antiprotease screen of the respiratory tract. Several pharmacological approaches have been investigated: 1) genetically engineered mutants of alpha,-AT and low-molecular weight elastase inhibitors; and 2) alpha,-AT that may be administered in sufficient quantities by infusion to replete deficient patients. BAL might be used to evaluate the efficacy of this therapy, to verify whether adequate enzyme concentrations are reached in alveolar lining fluid [278, 279].

**Conclusions**

In conclusion, in agreement with recent review articles [101, 198], we believe that there is no indication at present for the use of bronchoalveolar lavage for the diagnosis, staging or monitoring of chronic bronchitis and emphysema because of the lack of specificity of the findings from bronchoalveolar lavage fluid analysis. However, bronchoalveolar lavage from patients with mild or moderate airflow obstruction can be safely accomplished for the investigation of the mechanisms involved in the development of the disease.
Therapeutic applications of BAL

C. Danel, D. Israel-Biet, U. Costabel, L.M. Fabbri, H. Klech

Although BAL had been used for therapeutic purposes prior to its use as a diagnostic procedure and the value of BAL in the exploration and management of some interstitial lung diseases is now well established, its place in therapy is controversially reported. As early as 1963, RAMIREZ et al. [280] were the first to perform a whole lung lavage (WLL) using a large volume of fluid in patients with pulmonary alveolar proteinosis. Since then, this technique has been proposed to remove any alveolar filling material in conditions such as alveolar proteinosis [196, 281], alveolar microlithiasis [282], acute silicosis [283], or accidental inhalation of radioactive particles [289, 205]. Its use has also been proposed in obstructive lung diseases [286] to remove the mucus secretions accumulated in the bronchial tree in asthma [287, 288] or in cystic fibrosis [289, 290]. This lavage differs from the segmental BAL currently used for diagnostic or research purposes in that it is performed under general anaesthesia, and uses a much larger fluid volume. The actual procedure varies slightly from one centre to another and has not yet been standardized [196, 291]. WLL is a safe procedure as shown by the absence of chronic side-effects over periods as long as 25 yrs in patients treated for pulmonary alveolar proteinosis (PAP) [192]. On the other hand, its efficacy is known to be dependent on the type of disorder in which it is performed.

We will briefly review the main pathological conditions in which WLL is currently performed.

**BAL in alveolar proteinosis**

The benefit of therapeutic WLL is now well demonstrated in this disease. First proposed by RAMIREZ et al. [280], the technique has been slightly modified over the years. When the diagnosis of primary PAP is established, the decision to perform a therapeutic bronchopulmonary lavage should be based upon the patient's exercise tolerance and on his symptomatology, because spontaneous remission is always possible. When indicated, the performance of a WLL requires an experienced staff and considerable back-up facilities [196]. The first fluid samples to be recovered have a milky aspect which clears up progressively during the lavage. This treatment always improves the patient's symptoms [196, 281]. Some authors have shown a significant improvement of alveolar macrophage (AM) function after therapeutic WLL, demonstrating that the effect in AM function in PAP is reversible. Furthermore, this treatment could also reduce the rate of secondary infections [196, 281]. Although idiopathic forms of PAP are always improved by WLL, the periodicity of the need for therapeutic BAL varies widely from one patient to another, depending on the individual course of the disease.

In case the clinical symptoms do not dramatically improve after a whole lung lavage, a clinical and pathological search should be made for an associated condition; an open lung biopsy is then required to eliminate, for instance, acute silicosis, infections and/or malignancy [283, 293].

**BAL in asthma**

Mucus plugs are known to contribute to the severe hypoxaemia in patients with status asthmaticus due to large ventilatory defect. These plugs can be removed by suction through a bronchoscope after the instillation of saline or acetylcysteine [287, 288]. However, this procedure was thought to have a high risk/benefit ratio. Some investigators have markedly improved the benefit of this technique by limiting the indications and through technical modifications. Clinical benefit is likely if tenacious mucus plugging or tracheobronchial casts are present. Nevertheless, despite this study [288], it seems that WLL in patients with severe asthma must still be considered as experimental in nature and performed in selected patients, by well-trained physicians with an extensive experience in this field and only in the context of an intensive care unit.

**BAL in pneumoconiosis**

It is well known that inhaled inorganic dust damages the lung by inducing an inflammatory reaction that progressively leads to fibrosis. WLL has been proposed in order to remove the irritating dust before this irreversible damage occurs especially in the acute form of silicosis [294]. The lavage fluid is usually striking with its black or brown colour and numerous alveolar macrophages containing dust particles. It seems that the procedure results in rapid symptomatic improvement but without modification of the pulmonary function or the prognosis [294].

**BAL in inhalation of radioactive particles**

The benefit of WLL in human contamination is not yet clearly defined [284, 285]. Experimental studies on dogs and baboons have been carried out over the last twenty years to determine the efficacy of WLL in the removal of such particles. It seems that, although the longer the radioactive material is present in the lung, the greater the dose delivered, WLL should not be performed in the early stages of contamination since it can prevent the usual physiological clearance of inhaled particles from the upper respiratory tract. WLL seems to be indicated in levels of contamination inducing acute effects, while its value in patients with lesser exposure is not clearly established.
Other therapeutic applications of BAL

WLL has been proposed in the treatment of some other pulmonary disorders such as alveolar microlithiasis or exogenous lipoidosis, with some clinical but without any objective functional or radiological improvement [282].

In cystic fibrosis (CF), the benefit of WLL is also difficult to evaluate. It was expected that periodical repeated WLL could, if not arrest, at least slow down the progressive deterioration of lung function caused by the accumulation of bronchial secretions [289, 290]. Some authors have proposed WLL using antifungal drugs as a local treatment of aspergillosis, a frequent complication of CF [290]. This requires further investigation.

Conclusions

The therapeutic value of BAL is now perfectly established in alveolar proteinosis, which remains the only definite indication of this procedure. In other lung disorders, this technique still has a risk/benefit ratio which does not argue for its use in routine clinical practice. Its indication should be discussed for each patient and performed by an experienced staff in the context of an intensive care unit.

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Respiratory muscle fatigue

The International Meeting on Respiratory Muscle Fatigue was held in Florence (Italy) on March 8th–9th, 1990 with the sponsorship of 3rd Clinica Medica Institute (Florence University), Pro-Juventute Don Carlo Gnocchi Foundation (Florence) and S.E.P.C.R. Rehabilitation Working Group

G. Scano (Italy)

The aims of the meeting were to clarify the conditions and mechanisms involved in respiratory muscle fatigue and to critically assess relevant therapeutic strategies.

A. de Troyer (Belgium) reviewed the action and co-ordination of respiratory muscles. Rib cage and abdominal muscles function in parallel, during quiet breathing, to achieve uniform expansion. The dome of the diaphragm descends during inspiration by contraction of the vertical muscle fibres. This action helps the lower ribs to swing outwards and upwards.

In patients with cervical cord transection at C5, who breathe only with the diaphragm, the abdomen expands during tidal ventilation with the lower part of the rib cage. The upper part of the cage is sucked in. In the normal person, during normal tidal breathing there must be some action on the upper rib cage to prevent it from being drawn inwards. Electromyographic recordings demonstrate activity of the scalene muscles, which are not therefore solely accessory muscle.

Intercostal muscles are also important. There are three groups, the parasternals, the external intercostals and the levator costae. They are all active during tidal inspiration. In a series of dog experiments, involving selective section of the nerve supply to the three groups of muscles, the parasternals were determined to be by far the most important accounting for 80% of the movement of the upper rib cage. The muscles of tidal breathing are, therefore, the diaphragm, the scalenes and the parasternals, a view that many traditional physiologists might find surprising.

The amount of activity varies with body position. Parasternal inspiratory shortening is reduced in the upright standing position compared to the supine posture, but still plays a role in elevating the ribs despite the increased loading. The question of whether expiratory muscles contract during diaphragmatic tidal breathing was answered negatively.

M. Green (UK) reviewed respiratory muscle function and fatigue with an overall view that demonstrated the remarkable difficulty in proving the presence and extent of respiratory muscle fatigue in normal and pathological man. Symptoms and signs such as impaired cough, breathlessness, orthopnoea, repeated infection, weakness and wasting of intercostal muscles, paradoxical and chest wall movement are all highly nonspecific. Equally, vital capacity and other simple respiratory function tests such as lung volumes and carbon monoxide transfer coefficient (Kco) are nonspecific, although in certain circumstances vital capacity may be useful if the clinical situation and previous history are well known. Maximal inspiratory pressures (Pmax and maximal expiratory pressures are more specific but suffer the problem of a very wide range of normal values. Pmax can be as low as 30–50 cmH₂O when values are mostly >100 cmH₂O. Pressures of <80 cmH₂O in males, <60 cmH₂O in females, stand a high chance of being associated with respiratory muscle weakness. Other tests using gastric and oesophageal balloons measure transdiaphragmatic pressure (Pdi) and electrodes measure diaphragmatic electromyography (EMG). M. Green (UK) supported his use of the “Sniff test” for measuring diaphragmatic twitches as one of the best available measures of respiratory muscle function.

To evaluate nerve function, the phrenic nerve is stimulated percutaneously in the neck, and the transdiaphragmatic pressures measured. Conduction time of the phrenic nerve, also measured, is normally <10.5 ms from the stimulus artifact to the muscle action potential (MAP).

Respiratory muscle fatigue is more difficult to evaluate. The following techniques, not available for use in the clinical setting, are being studied: a) frequency-force curve of the diaphragm to measure low frequency fatigue (LFF) and high frequency fatigue (HFF); b) power spectrum electromyogram of the diaphragm or intercostal muscle to calculate the H/L ratio; and c) relaxation rate of a single diaphragmatic sniff or phrenic twitch particularly in Intensive Care Units. Low frequency stimulation is very unpleasant for both normal subjects and patients, and HFF is difficult to interpret in a clinical setting. The relationship between H/L ratio and LFF is still unclear. The tests are not easy to use and thus precise recognition and quantitation of fatigue changes remain elusive.
Respiratory failure is either acute or chronic in onset. Expected to function, the lung volume at which the respiratory muscles are available through oxygen supply, blood flow and energy substrate. The balance of fatigue is markedly shifted by the lung volume at which the respiratory muscles are expected to function.

Increasing lung volume increases energy demands. Respiratory failure is either acute or chronic in onset. Acute failure passes through a stage of normal breathing to tachypnoea, than bradypnoea and finally output failure. In chronic respiratory failure, the process takes several years, with tachypnoea and low tidal volume being the most extended stages. The concept of respiratory muscle fatigue in chronic obstructive airways disease and chronic muscle disorders has been promoted by various authors. It gave rise to a number of studies which looked at external negative pressure ventilation as a means of achieving respiratory muscle rest. Indicators such as dyspnoea, maximal inspiratory and expiratory pressures, diaphragmatic EMG and Pdi were measured. The results were unconvincing in terms of both physiological and clinical benefit.

A. Grassino (Canada) discussed approaches to therapy involving a number of basic principles. Firstly, to deal with toxicity from such sources as sepsis, acidosis and heart failure. Ensure good nutrition and consider drugs such as theophyllines, β₂-agonists, oxygen and digitalis to enhance muscle function. Studies by Aubier (France) and J Moxham (UK) using aminophylline produced conflicting results for respiratory muscle fatigue, probably because clinical conditions, patients, and techniques differed. The effect of aminophylline is not dramatic, but β₂-agonists are promising. They may improve respiratory muscle endurance and/or recovery time from fatigue. When the diaphragm is forced into strenuous activity, hypoxia or a combination of hypoxia and hypercapnia may impair contractile force. In his series of 300 chronic obstructive pulmonary disease (COPD) patients, an airs resistance maximal inspiratory pressure (Raw/MIP) ratio of 0.3-0.4 related to CO₂ retention. When chronic CO₂ retaining patients enter a state of acute respiratory failure, a decision has to be taken as to whether the respiratory muscles are overloaded and liable to failure or, whether ventilation/perfusion (V/Q) mismatching is the major explanation of deteriorating blood gases. Both causes may be present and it is difficult to apportion responsibility. If respiratory muscles do not provide sufficient ventilation and there are strong suspicions of fatigue, they need to be rested. Respiratory muscle rest, although theoretically of value, remains a contentious issue. If a ventilator is used to support respiration suitable operating pressures are selected and the patient must not fight the system.

High positive expiratory pressures shorten the diaphragm and reduce transdiaphragmatic pressures. The iron lung is a good means of treating comatose patients. Blood gases are corrected but excessive hyperventilation will create weaning problems. It may be necessary to control the treatment using EMG and Pdi measurements. Improving hypoxia and reducing hypercapnia are generally thought to be worthwhile.

For long-term prevention of respiratory muscle fatigue there are theoretical benefits in training the force and endurance of respiratory muscles and diaphragm but such suggestions are by no means of proven value.

S. Cibella (Italy) discussed the applicability of EMG spectral analysis to respiratory pathophysiology and the detection of respiratory muscle fatigue. Many indices, derived from EMG spectral analysis have been used to detect fatigue, but central frequency (cf) has the lowest coefficient of variability. Unfortunately, some experimental and biological variables time elapsed from the beginning of the contraction and length of the EMG portion under analysis can determine changes in the EMG power spectrum and central frequency independently of fatigue. Variations in fibre length occur continuously in the diaphragm due to changes in lung inflation and abdominal configuration. The influence of these variables on cf obtained from the diaphragmatic EMG demonstrates that abdominal thoracic configuration has an important influence on cf at least at the lowest levels of lung inflation.

P. Howard (UK) discussed the use of external negative pressure ventilation (ENPV) particularly in patients with obstructive airways disease and respiratory failure. It is not clear from the literature what is to be expected of external negative pressure ventilation. There are two views, firstly to relieve respiratory muscle fatigue and secondly to improve blood gases. The two features were not necessarily associated. A review of the literature pointed to the remarkable difficulties of measuring respiratory muscle fatigue in COPD patients. Highly inconsistent results are obtained but probably the most widely used test is diaphragmatic EMG.

It is important to capture the ventilatory rhythm of patients whatever system of external negative pressure ventilation is selected, Ponecho, pneumowrap or cuirass. In COPD, the pressures need to be negative of the order of 20-25 cmH₂O at a ventilatory rate one or two breaths per minute above the patient's resting frequency. No clear benefit to respiratory muscle fatigue or improvement of the sensation of dyspnoea has been observed. The large Montreal study, which attempted to relieve dyspnoea in severe bronchitics using ENPV, apparently produced negative results. The machines were found to be uncomfortable and intolerable beyond one or two hours of use.

As a means of improvement of blood gases, more consistent results are obtained. Short periods of daytime or nocturnal ventilation in bronchitics might be useful, but consistent improvement is more often seen in neuromuscular respiratory failure. Care has to be taken when using external negative pressure ventilation.
in hypoxic bronchitics to avoid exaggeration of obstructive sleep apnoea.

D. Rodenstein (Belgium) reviewed the use of the new technique of ventilatory support, i.e. nasal intermittent positive pressure ventilation. He stressed that a detailed evaluation of individual patients, whether they suffer from COPD or neuromuscular ventilatory failure, is essential. This necessitates not only respiratory function measurements and blood gases but also measures of maximal inspiratory and expiratory pressures and tests of diaphragmatic function. The use of the various types of assisted ventilation should be judged against the results of these indicators. In the sleep apnoea syndromes, continuous positive airway pressure (CPAP) is undoubtedly the best form of therapy. In restrictive lung disease with neuromuscular failure, assisted ventilation with cuirass might give the best results. In COPD, the situation is much more difficult. Patients do not easily accept cuirass ventilation. Intermittent nasal pressure ventilation has been applied with benefit in acute exacerbations and in one or two patients over a longer-term but the major difficulty is still to get patients to accept assisted ventilation. Long-term domiciliary oxygen therapy should always be tried first and may well be the only option for many patients.

A. Rossi (Italy) summarized the treatment of ventilatory pump failure stressing the need to optimize drug therapy and relieve, as far as possible, systemic disease and reversible respiratory disorder. In chronic obstructive airways disease, the importance of PEEP during ventilatory support in acute ventilatory failure was stressed for flow-limited patients. External PEEP must be less than intrinsic PEEP. The management of carbon dioxide retention, the use of mechanical ventilation and the problems of weaning, reduction of ventilatory load by relief of bronchoconstriction, treatment of infection and thick mucus and the addition of extrinsic PEEP to flow-limited patients were all reviewed. In his view, the use of both aminophylline and adrenergic agonists were associated with a significant increase in maximum transdiaphragmatic pressure in COPD patients. The improvement was not fully explained by changes in lung volume. Other mechanisms, such as a direct action on the muscle fibre or a local increased blood flow to the diaphragm, need consideration. Selective approaches titrating therapeutic options to the patient particularly in COPD were stressed.

It is clear from the last three papers that no easy therapeutic solution to the problem of respiratory failure in COPD yet exists.

N. Pride (UK) discussed respiratory muscles in neurological disorders such as ataxic quadriplegia, motor neurone disease, old poliomyelitis and disseminated sclerosis, neuromuscular disorders such as myasthenia gravis and muscle disease such as dystrophia myotonica and the dystrophies. When the only abnormality of the respiratory system is known to be respiratory muscle or neurological disease then vital capacity is a reasonable indicator of prognosis. Total lung capacity and functional residual capacity (FRC) are diminished and the pattern of breathing is one of rapid shallow breaths. In all muscle disorders there is marked inspiratory muscle weakness with MIP generally less than -40 cmH2O. There is a dispute as to whether one should measure the pressure during a cough or a sniff. In these disorders supportive ventilation has generally given good results on blood gas improvement, the non-invasive method of nasal positive pressure ventilation and cuirass negative pressure ventilation being far more successful than in COPD. There was less certainty about improvement of respiratory muscle weakness. In early stages of the disease, disproportionate muscle weakness associated with respiratory failure, given a period of daily ventilation may lead to a successful prolongation of life.

C. Donner (Italy) discussed respiratory muscle management in rehabilitation. In obstructive airways disease, hypoxia and mechanical distortion of the thoracic cage give rise to increased ventilatory need which may be associated with dyspnoea and possible muscle fatigue. Any method of increasing ventilation by the patient involves more energy expenditure. A number of options are available for rehabilitation to try to bring the balance between energy need and supply closer. Measures of improving hypoxaemia by treatment of bronchoconstriction and infection and supplemental oxygen should be undertaken. Diaphragmatic training, whole-body exercise and specific inspiratory muscle training are available. Whole-body training had little effect on respiratory muscles. Specific inspiratory muscle training has more potential but care has to be taken to ensure that the necessary inspiratory muscle pressures are achieved during the training programme. Studies are still proceeding. Thus, for the treatment of respiratory failure external negative pressure and nasal ventilation are options. It was still not clear whether in the longer-term these are any better than tracheostomy and intermittent positive pressure ventilation. In all cases blood gases improve. Long-term domiciliary oxygen therapy (LTOT) is the first method of treatment and when this fails the other options are available. Tracheostomy and IPPV should not necessarily be rejected at this stage.

Problems of nutrition lead to negative energy balance and muscle wasting in COPD. It may be necessary to increase caloric intake to 30% above baseline levels. This is difficult due to loss of appetite and intolerance of normal food intake. There is clearly a need for further research in this area.

R. Sergysels (Belgium) reviewed the application of physiotherapy to rehabilitation, questioning whether alteration of breathing pattern could usefully improve energy conservation, relieve muscle fatigue and achieve less dyspnoea. Several techniques of breath training had been suggested to include low frequency breathing, abdomino-diaphragmatic breathing and body positional change. There was no evidence, despite many claims in the literature, that any of the directed breathing techniques could lead to a permanent change of breathing pattern. Many of the low frequency types of breathing and abdomino-diaphragmatic breathing which change
breathing pattern by increasing inspiratory time as a fraction of total breath duration (Ti/Ttot) may induce fatigue in patients with severe airflow obstruction.

The only body position that significantly decreases FRC in normal subjects and COPD patients is the supine position. Few patients describe a decrease of breathlessness when so positioned and prefer to adopt a forward sitting position. In the latter position, an increase in FRC occurs in normal subject and in some COPD patients making it difficult to explain the relief of dyspnoea. The effect of body position on dyspnoea remains unexplained. These techniques should not be included in rehabilitation programmes until further information is available.

In the free papers, maximum transdiaphragmatic pressures were studied in normal persons. It was felt possible to produce diaphragmatic fatigue after vigorous exercise but recovery was quick and certainly within 30 min during resting conditions. Maximum Pdi fell due to changes of gastric pressure. It was not clear why this should be so. Diaphragmatic EMG measured in relation to respiratory fatigue and neurorespiratory drive was found to indicate respiratory drive more accurately than mouth occlusion pressure (P_{EO}) in COPD. Two papers reviewed the treatment of acute and chronic ventilatory failure in COPD with nasal intermittent positive pressure ventilation; benefit was claimed.
From alveoli back to bronchi: new perspectives of bronchoalveolar lavage

An International Workshop was held at the Medical Centre of Rehabilitation, Veruno (NO), Italy, April 19th–21st, 1990. Organized by Clinica Del Lavoro Foundation, Pavia, Italy. Sponsored by S.E.P.C.R. Rehabilitation Working Group and Associazione Italiana Pneumologie Ospedalieri (AIPO), Italy.

C. Donner (Italy), P. Howard (UK)

The Bronchoalveolar Lavage Conference 1989 investigated the possible uses of the technique and applications were define in obstructive airways disease, the diagnosis of pulmonary infection, particularly in immunocompromised patients, the investigation of malignancy and lung toxicity. This year, the discussions were focused more on asthma, bronchitis and cancer. This restriction is testimony to the increasing scientific application of the technique evident during the two day proceedings.

**BAL and asthma**

Inflammation of the airways has long been accepted as a fundamental part of the asthma mechanism, but to those not closely involved with bronchoalveolar lavage (BAL) continuing inflammation of small airways has not been an appreciated feature of bronchitis. This inflammation contrasts with the clinical manifestations of occasional attacks of green sputum and pyrexia which are quickly controlled with antibiotics. In a number of patients a more sinister long-term inflammation of the bronchioles continues, causing progressive tissue destruction. It is here that the contrasts with bronchial asthma are marked, where despite years of florid inflammation few patients proceed to destructive and permanent airway change. In bronchitis a proportion of hospital patients seem to undergo a progressive decline, as judged by spirometry, which is given no more than temporary relief by current therapeutic applications. Fletcher et al. (1976) [1] studied early bronchitis in postmen and found it to be largely related to smoking, and to subside after cessation of the habit. This suggests that bronchial inflammation in bronchitis, like that in asthma, need not necessarily lead to destructive disease. What is it that triggers airway destruction in bronchitis and to a lesser extent in bronchial asthma? We know of a number of trigger factors, viral infection, perhaps also bacterial infection, tobacco smoke in susceptible persons and damaging fume of an overwhelming nature. The Bhopal disaster in India is a good example of the latter and there must be others. Therefore, airway inflammation was appropriately considered in more detail. In the first paper by Foresi (Italy), remarkable concordance was observed between cells produced by bronchoalveolar lavage (BAL) and cells in biopsy specimens found in the wall of inflamed bronchi. It has always been worrying that bronchoalveolar lavage does not reliably reflect the happenings in the adjacent airway. Reassurance was evident in this paper. Bronchial hyperresponsiveness is also associated with an inflammatory reaction, but it must be different from that associated with bronchial asthma as the asthmatic expression has still not occurred.

Many technical problems remain in the BAL procedure. Walters (UK) and Klech (Austria) reminded us of the difficulties of dilution, the treatment of cells and the sequence and volume of lavages. Whilst it is accepted that many studies employ techniques developed in individual departments a plea was made for adherence to the standardization of techniques already printed through the auspices of the SEP Bronchoalveolar Lavage Working Party [2]. This will make it easier to compare the work of different departments.

The importance of high dose aerosolized steroid treatment of bronchial asthma was emphasized by Walters (UK). Interestingly, the good clinical response was not mirrored by a concurrent reduction of inflammatory cells and other measurements in BAL. There were questions as to the relevance of the florid manifestations of airway inflammation in bronchial asthma to the associated bronchoconstriction.

BAL in bronchial asthma is associated with increasing numbers of neutrophils, eosinophils, lymphocytes and macrophages. There seem to be different patterns, different sorts of asthma and differences at various stage of the disease. Godard (France) felt that the macrophage was the central cell to which the induction and activities of the other cells relate. This was not
universally agreed, others pointed to the respective importance of the other cells. G. Rossi (Italy) examined inflammatory cells and their activity in small airways and alveoli. He questioned whether low aliquot BAL truly reflects airway pathology alone. However, the idea that inflammation at the two sites, bronchi and alveoli, might be different was well accepted. He suggested an early release of eosinophils with production of specific immunoglobulin E (IgE) as a first phase in the asthmatic reaction.

**Chronic bronchitis**

Jeffery (UK) outlined the pathological differences in the airway of the asthmatic and the bronchitic. He considered morphological, microscopic and cellular changes. There were marked differences between bronchitis in asthma and chronic bronchitis in terms of airway size, mucosal disruption, smooth muscle hypertrophy, characteristics of mucus and the pattern of inflammatory cells. Such differences must point to differences in consequence of the inflammatory reaction.

A number of papers looked at the components of airway destruction in bronchitis. Costabel (FDR) described a suppression of immune response of alveolar macrophages in smokers and pointed to increased levels of oxidized methionine in bronchitics with airway obstruction, noting no differences in this measurement between smokers and nonsmokers in the absence of airways obstruction. This was interesting, as it suggested that some specific change had occurred in those patients reacting adversely to the smoking habit.

In subsequent papers the mechanisms of oxidant-antioxidant balance, protease-antiprotease balance and deficiency of surfactant were considered. All may contribute to progressive airways destruction. Oxidants were classified as either endogenous or exogenous in origin. Therapeutic intervention might stimulate, respectively, the patients endogenous antioxidant sources or add exogenous therapy by means of tablets or aerosols, preferably the latter.

Similar discussion reviewed the concept of excess alveolar protease, which was thought to contribute to destructive emphysema. The principle consequence is a deficiency of alpha,-antitrypsin (α,-AT) in epithelial lining fluid, allowing digestive destruction of small airways and alveolar walls. In a masterly exposition, the work of the National Institute of Health in Bethesda, Maryland, on alpha,-antitrypsin substitution therapy was detailed by Hubbard (USA). Intravenous weekly or monthly injections of human α,-AT or inhalation of recombinant α,-AT through aerosols were considered. The prospects for the therapeutic use of recombinant α,-AT are increasing. It is possible to achieve adequate blood levels and, therefore, to replace α,-AT deficiency in patients with congenital defects and cystic fibrosis, the latter having an overwhelming neutrophil load with consequent protease excess in small airways and alveoli. It has not, as yet, been possible to translate α,-AT replacement to undoubted evidence of clinical benefit, but hopes are high for current trials. These are being conducted in congenital α,-AT cystic fibrosis and chronic obstructive pulmonary disease.

Lusuardi (Italy) reviewed the role of surfactant on maintenance of airway integrity, airway defence, control of small airway infection and inhibition of tissue destruction. Two therapeutic applications should be considered: replacement of lost surfactant in chronic obstructive pulmonary disease (COPD) and related conditions and stimulation of natural surfactant production by drugs such as Ambroxol. In the first studies of Ambroxol, no clear ability to increase the phospholipid pool in the lung was realized but these are early investigations. Both the dose and the dosage schedules might be incorrect, and work must continue in this important area.

**BAL and cancer**

Three aspects of this topic were considered: detection of cancer with a view to prevention, investigation of carcinogenic mechanisms, and monitoring of therapy through adjustment of manipulation of the function of recovered BAL cells.

Izzotti (Italy) described a fascinating investigation of the attachment of carcinogens to nuclear material of pulmonary alveolar macrophages (PAM). It is possible to detect benzpyrene attached to deoxyribonucleic acid (DNA) in smokers. This is an exciting discovery as it suggests detection of cancer prone persons might be possible, opening the way to preventive chemotherapy. Questions were raised as to how long the carcinogen might stay attached to the nuclear material of PAM's why some heavy smokers succeeded in avoiding such DNA attachment, and the mechanism by which PAM carcinogen affected tumour formation in neighbouring epithelial or glandular cells.

A discussion of the importance of epithelial metaplasia as a pre-cancerous lesion in the lung followed. Metaplasia was found to be associated with airway inflammation from a wide range of trigger factors. Airway inflammation has carcinogenic potential. Cellular function associated with this type of airway inflammation appeared to be slightly different from that associated with bronchial asthma and the destructive lesions of bronchitis. The consequences of the functions of inflammatory cells will differ quite markedly from one situation of inflammation to another. BAL has a major potential to examine the function of individual cells and provide a new horizon for the method. Investigation of these functions is less dependent on the details of technique necessary for counting cells.

The diagnostic value of BAL was reviewed. In conjunction with skilled cytology it is now possible to achieve 60–70% positive diagnostic yield for lung
cancer. Further work needs to be undertaken to define the precise use of BAL in cancer diagnosis. When bronchoscopy reveals an obvious tumour in the main airways for which biopsy is performed or an obvious peripheral lesion in which it is easy to place a needle, BAL is less important. For diffuse lesions of doubtful aetiology there is an important and developing application.

More detailed examinations of lymphocyte and macrophage function yielded complex and disparate findings. It is difficult, as yet, to identify a clear channel through which these studies might contribute to the therapy or diagnosis of cancer except to re-emphasise that cancer associated cells are functionally different from those in the inflammation associated with bronchitis and asthma. An investigation of tumour necrosis factor, produced by pulmonary alveolar macrophages, showed this substance to be reduced by prostaglandin E₂. Prostaglandin E₂ was found to be in high concentration in a number of lung cancers. Perhaps the tumour cells can turn-off one of their destructive opponents. Investigation of cellular function, by use of BAL, after cancer chemotherapy or cancer immunotherapy has started.

Conclusion

In summary, this Conference showed that the scientific aspects of BAL are being focused on aspects of inflammation in asthma, bronchitis and cancer. Inflammation is clearly not a uniform condition and cellular function within it is variable. We are reminded that twenty years ago, at the birth of modern immunology, lymphocyte function remained an enigma as all of the cells looked alike. Measurement of subset function is now common-place. The same process, it would seem, will develop for inflammatory cells. BAL is ideally placed to be the modern tool of this new science.

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