Table I – Principal disorders associated with diffuse pulmonary haemorrage (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 lymphangiomyomatosis.
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 mm^3 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

Lymphocytic	Neutrophilic	Eosinophilic
Methotrexate	Bleomycin	Bleomycin
Azathioprine	Busulphan	Nitrofurantoin
Bleomycin		Cotrimoxazole
Busulphan		Penicillin
Nitrofurantoin		Salazopyrin
Acebutolol		
Gold salts		
Salazopyrin		
Amiodarone		
Propanolol		
Diphenylhydantoin		

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 lipoid 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, 2189]. 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.