Role of bronchoalveolar lavage in the assessment of pulmonary complications following bone marrow and organ transplantation

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Transplantation is a major therapy for many diseases. Neoplastic and non-neoplastic diseases are treated with bone marrow transplantation. Failure of parenchymal organs has been treated with specific organ transplant. Combination transplantations have been undertaken. Transplantation stresses the lung and pulmonary complications frequently develop. Bronchoalveolar lavage (BAL) is valuable in assessment and management
of transplant patients. Pulmonary complications arising from transplantation include: 1) effects of immunosuppression; 2) immunological reactions; 3) drug toxicity; and 4) "special problems".

Immunosuppression is generally required for transplantation and infections, including those by opportunistic organisms, are frequent. BAL is important in assessment of pulmonary infection because: 1) each lavage can sample approximately one million alveoli and a wedged lavage can be performed in several different segments during the same procedure, providing effective assessment of intra-alveolar infection; 2) BAL is relatively safe and easily performed compared to other invasive methods used to obtain diagnostic material such as transbronchial or open lung biopsy. Use of BAL is important in thrombocytopenic patients where bleeding represents a potential hazard; with BAL, bleeding seldom occurs even in severe cases [1]. No serious bleeding complication occurred in over 1,000 BAL performed in bone marrow transplant patients, many of whom were severely thrombocytopenic.

We perform bronchoscopy and BAL at an "early" stage in transplant patients, i.e. when their clinical condition suggests possible lower respiratory tract infection. This aggressive use of BAL often yields a diagnosis before respiratory failure develops, i.e. when the patient can better tolerate the procedure and when antibiotic therapy is most helpful. Transbronchial biopsy is not generally performed as it increases morbidity and mortality without dramatically increasing yield. Results of initial BAL are available within hours and the procedure can be repeated with or without transbronchial biopsy when required. If no diagnosis is obtained, open lung biopsy can follow. Aggressive use of BAL causes little delay in proceeding to open lung biopsy if needed, which is rare with this approach.

Various techniques increase the diagnostic power of BAL [2]. Cytological evaluation using a rapid silver staining technique is highly effective in diagnosis of Pneumocystis carinii and fungal infections. However, aspergillosis is frequently present in the vascular spaces of the lung but not the alveoli and, thus, often not recovered by BAL. Candida is often found in BAL as a contaminant from the oropharynx. Although diagnosis of candida pneumonia by BAL is difficult, the number of organisms seen cytologically, clinical circumstances and tests such as quantification of candida antigen in BAL are helpful [3]. Cytology using PAP techniques can assist in diagnosis of a variety of viral infections. Special diagnostic studies are available including immunohistochemical stains and probes using viral specific cDNA. With the advent of antiviral antibodies, accurate diagnosis and prompt treatment of viral pneumonias can greatly aid the clinical management of transplant patients.

BAL yields a diagnosis of bacterial pneumonia [4, 5] of comparable accuracy to that of sheath catheter culture, transtracheal and transthoracic needle aspiration and endotracheal suctioning. Use of quantitative culture may be helpful in confirming the diagnosis particularly in a complex transplant patient with a severely abnormal chest X-ray and several potential non-infectious processes. Quantitative BAL may have implications similar to those of quantitative urine cultures.

Immunologically mediated lung disease can occur in at least two analogous settings. Following lung transplantation, the host immune system can recognize the donor lung as foreign leading to rejection, which may be acute, hyperacute or a chronic form of rejection leading to bronchiolitis obliterans [6]. In allogeneic bone marrow transplantation, the donor derived lymphoid cells can attack the host lung. Although the lung does not normally appear to be involved in classic acute graft-versus-host disease (GVHD), the syndrome of idiopathic interstitial pneumonitis developing within 100 days of allogeneic transplantation is much more frequent in patients with GVHD [7]. Chronic disease can develop in these patients and lead to the development of bronchiolitis obliterans [8]. This may be a major source of long-term morbidity and mortality in both lung and allogeneic bone marrow transplantation.

It has been suggested that the bronchiolar epithelium participates in the response to infection by recruiting lymphocytes expressing MHC antigens [9] and genes [10]. Perhaps such "activation" of the epithelial cells leads to their recognition by non-identical lymphocytes. BAL will help in exploring such concepts. The major role of BAL at present is to exclude a treatable infection. BAL could be used to monitor the severity of lower respiratory tract inflammation by lavage differential or quantification of antigen specific lymphocyte activation [6] and, thus, assist in determining anti-inflammatory therapy.

Drugs used in transplantation can cause pulmonary toxicity, e.g. GMCSF, used to speed recovery of marrow function following transplantation, and OKT-3, used to treat acute rejection, have been associated with symptoms like those of adult respiratory distress syndrome (ARDS). Cytotoxic anti-cancer chemotherapy used in bone marrow transplantation can injure a variety of non-neoplastic cells including those of the lung.

A syndrome characterized by progressively severe diffuse alveolar haemorrhage developing about 14 days after autologous bone marrow transplantation appears to be a major cause of mortality. The prominent pulmonary features of the syndrome have led to the use of the name DAH (diffuse alveolar haemorrhage). The pulmonary parenchyma and that of other organs appears to be affected. The condition resembles thrombotic thrombocytopenic purpura but with no evidence of microangiopathic intravascular haemolysis. No coagulopathy is present but platelet consumption is prominent. Fever, renal failure, CNS dysfunction and diffuse pulmonary infiltrates progressing to respiratory failure are common. No infectious agents are identified. The findings on BAL are characteristic: each successive aliquot of fluid lavaged at a single wedged site yields retama that are progressively bloodier. Successive aliquots are rich in alveolar material and little or no blood is recovered in a bronchial wash, hence the bleeding is alveolar. This has been confirmed at autopsy. The process is diffuse since lavages in separate lobes yield identical findings, often despite normal chest X-ray in the corresponding region.
Pulmonary toxicity induced by chemical agents

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Pulmonary toxins include a spectrum of agents from clinically useful drugs to environmental pollutants. Many probably cause lung damage at a cellular level in a similar manner (table 1). Better understanding of this mechanism improves the diagnostic and therapeutic approach to patients with serious pulmonary reactions to toxins.

Supplemental oxygen is a well-known therapeutic agent, associated with significant pulmonary toxicity when used in concentrations exceeding 50–60% for a long period. Although hyperoxia has been shown to be directly toxic to lung parenchymal cells [1] there is clear evidence to implicate the inflammatory response in the mediation of oxygen toxicity [2, 3]. There is increasing evidence for direct and indirect mechanisms operating in the development of pulmonary toxicity.

References

Oxygen is the ultimate electron acceptor in aerobic metabolism, with its eventual reduction to water. The cell must "handle" O₂ carefully using a divalent reductive process in the cytochrome system, since univalent reduction of O₂ results in generation of potentially lethal O₂-derived species such as superoxide, hydrogen peroxide and the hydroxyl radical. The cell has derived a variety of defence systems to protect the cell. Normally the antioxidant defences are available in excess and generation of occasional O₂-derived radicals is no risk. In conditions where their generation is facilitated, i.e. hyperoxia, parquat toxicity, bleomycin toxicity etc., these agents induce a variety of biochemical insults to the cell such as lipid peroxidation, cell membrane damage, DNA damage (inhibited or altered replication) or attack of sulphydryl bonds (proteins destruction). A large variety