Lung allograft transplantation: indications, preoperative assessment and postoperative management

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ABSTRACT: In spite of a shortage of available donors, an increasing number of heart-lung transplantations have been performed within the last decade. This procedure, first limited to patients with pulmonary vascular disease, has been successfully extended to patients with end stage lung disease, including cystic fibrosis. More recently, single lung, double-lung and bilateral single lung transplantation have become other therapeutic options.

Better selection of patients and donors as well as improvement in surgical techniques and immunosuppression regimens have contributed to the reduction in the high perioperative mortality experienced in the early stages. Moreover, the introduction of daily spirometry and transbronchial lung biopsies have permitted early and reliable diagnosis of opportunistic infection and rejection.

The most serious late complication of lung transplantation is obliterative bronchiolitis and further research is urgently required to improve diagnosis and management of this condition.
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Heart-lung transplantation

Since 1981, successful heart-lung transplantation with long-term survival has been achieved and today more than 500 have been carried out throughout the world [1–5]. During the early stages, the perioperative mortality was high, and obliterative bronchiolitis leading to death or severe functional impairment developed in half of the long-term survivors [6]. In the past few years, decreased perioperative mortality and earlier detection of rejection and infection have permitted improved survival after heart-lung transplantation and actuarial survival rates ranging from 60–78% for one year and from 60–73% for two years have been reported [4, 7–9]. Between 1981 and 1985, most recipients had advanced pulmonary hypertension related to Eisenmenger's syndrome or primary pulmonary hypertension [2, 6, 10]. More recently, an increasing number of patients with end stage lung disease have been successfully treated by heart-lung transplantation (table 1) [3, 4, 7, 11]. The most important difference distinguishing heart-lung from single or double lung transplantation ensues from the existence in normal individuals of relatively rich anastomoses between the coronary and bronchial arteries [4, 5]. These coronary to bronchial collaterals are not disrupted by heart-lung transplantation and the healing of tracheal anastomoses is more reliable

[8, 12]. Double lung and heart-lung transplantation both ensure the removal of all diseased tissue in patients with suppurative lung disease. To optimize the organ supply, the native recipient's heart, when normal, can be transplanted into another patient, and this so called "domino procedure" allows two recipients to benefit from the one original set of donor organs [4, 13].

Single lung transplantation

Until 1983, no long-term clinical success had been achieved by unilateral lung transplantation. Most of the early deaths had been related to infection, rejection and ischaemic disruption of the bronchial anastomoses [14, 15]. Successful unilateral lung transplantation was then carried out in Toronto, the success being attributed to the following factors: a) accurate selection of patients; b) withdrawal of corticosteroids in the early postoperative period and; c) omental pedicle wrapped around the bronchial anastomoses to ensure revascularisation and to avoid bronchial anastomotic complications [16–21]. However, more recent clinical experience [22] including a randomised trial from Harefield have shown no difference in bronchial healing in patients with or without bronchial wraps (unpublished data).

Table 1. – Indications for heart-lung, double-lung and single lung transplantation. Different therapeutic options for the same pathology point out the divergent opinions between centres

	Primary indications	Other options
a) Pulmonary vascular disease:		
– Eisenmenger's syndrome	HLT	SL*
– Primary pulmonary hypertension	HLT	DL*, SL*
– Thromboembolic pulmonary hypertension	HLT	
– Complex pulmonary atresia	HLT	
– Pulmonary veno-occlusive disease	HLT*	
b) Primary lung disease:		
– Cystic fibrosis	HLT	DL
– Emphysema	SL	HLT, DL
– Cryptogenic fibrosing alveolitis	SL	HLT, DL*
– Occupational lung disease	SL	DL
– Sarcoidosis	SL*	HLT*
– Bronchiectasis	HLT*	DL*
– Eosinophilic granuloma	HLT*	DL*
– Bronchiolitis obliterans	SL*	HLT*, DL*
– Lymphangioleiomyomatosis	SL*	HLT*
– Alveolar cell carcinoma	HLT*	
– Adult respiratory distress syndrome	SL*	

HLT: heart-lung transplantation; DL: double-lung transplantation; SL: single lung transplantation. *: limited experience.

Single lung transplantation was first performed in patients with fibrotic lung disease such as cryptogenic fibrosing alveolitis, sarcoidosis and eosinophilic granuloma. In those patients, increase in elastic recoil and vascular resistance of the remaining fibrotic lung ensured a progressive shift of alveolar ventilation and lung perfusion from the native to the transplanted lung [17, 23].

In contrast, patients with emphysema were considered unsuitable recipients for single lung transplantation [17]. This attitude was founded on the risk of overexpansion of the remaining emphysematous lung leading to· compression of the transplanted lung [14]. Furthermore, an early study demonstrated increased perfusion with decreased ventilation of the implant leading to an unacceptable pulmonary shunt [24]. However, more recent experimental and clinical studies have not confirmed the occurrence of ventilation-perfusion imbalance after single lung transplantation in emphysematous recipients unless rejection or infection developed in the transplanted lung [25–27]. In particular, it was shown by ventilation-perfusion scintigraphy that the allograft was perfused and ventilated adequately with a satisfactory matching of ventilation to perfusion [26, 27].

The value of single lung transplantation for primary pulmonary hypertension and Eisenmenger's syndrome is currently being assessed by several groups [28–31].

Several advantages characterize single lung transplantation. First of all, this procedure allows the surgeon to optimize organ utilization since the heart and the two lungs from a donor can be transplanted into three different recipients [32]. The risk of intraoperative and postoperative bleeding is lower since the surgical procedure is easier, the less affected side can be chosen in patients with pleural adhesions and cardiopulmonary bypass, with its associated complications, can often be avoided [4, 18, 26, 27, 33]. Disadvantages of single lung transplantation are related to the remaining diseased lung, the smaller margin of safety during rejection or infection, and possibly the smaller improvement in functional capacity. Furthermore, bronchial anastomotic complications remain frequent [18, 34, 35]. These issues need to be clarified in the future.

Double-lung transplantation

Patients with obstructive or septic lung disease may be suitable recipients for double-lung transplantation providing right ventricular function is adequate or recoverable [34]. During this procedure, both the recipient's lungs are removed and replaced by donor lungs, and the classical "en bloc" bilateral lung transplantation requires a tracheal, an atrial and a pulmonary artery anastomoses [36–39]. To avoid frequent ischaemic airway complications, this surgical technique has first been modified by using two main bronchial anastomoses instead of a tracheal one [34, 40], and recently, successful bilateral single lung transplantation has been achieved via either a transverse thoracosternotomy or using two lateral thoracotomies [41]. A valuable advantage of this latter technique is that cardiopulmonary bypass is not necessary.

Compared to heart-lung transplantation, double-lung transplantation has the advantage of preserving the recipient's heart. However, clinical experience with this procedure is still limited and further development of the technique should aim to reduce the high incidence of severe or even fatal airway complications [34].

Preoperative assessment

Patients disabled by pulmonary vascular disease or by deteriorating chronic respiratory failure (New York Heart Association Class III or IV) with a limited life expectancy, could be suitable candidates for allograft lung transplantation [5, 42]. Because of the shortage of suitable donors, lung transplantation should be offered to patients capable of full rehabilitation [43]. In most centres, recipient's age at heart-lung transplantation is around 20–30 yrs [3, 7, 8, 11, 42, 44]. Theoretically, there is no lower age limit, and very young children have been successfully transplanted [45]. However, in our own experience the incidence of obliterative bronchiolitis appears to be significantly higher in children below the age of 5 yrs. Thus, in this age group lung transplantation should be considered only when there is no alternative therapy. The upper age limit may be about 50 yrs for heart-lung and double-lung transplantation, while patients up to 60 yrs may be assessed for single lung transplantation, providing they have no evidence of other serious end organ dysfunction [17, 43]. Patients with end stage lung disease due to systemic disorders like systemic lupus erythematosus or systemic sclerosis may theoretically be candidates for lung transplantation. However, other underlying abnormalities, in particular renal involvement, often preclude transplantation.

As immunosuppressive therapy may increase the risk of malignancies, patients with a history of cancer should have a disease-free interval of at least five years [17]. A stable social and psychological background is also essential.

In the early studies, the high operative and postoperative mortality rates in heart-lung transplant recipients were mostly related to bleeding complications, especially in those with previous thoracic surgery and pleural adhesions [8, 11]. Today, patients with a previous thoracotomy still carry a higher risk of complications during the operation and pleural adhesions should be carefully assessed by computed tomography scanning before the transplant [8, 43]. However, patients with a high risk of bleeding may benefit during the surgical procedure from the use of aprotinin (Trasylol) [46, 47].

Systemic steroids can induce poor healing of the tracheal anastomoses and ideally they should be reduced to less than 7.5 mg·day^{-1} of prednisone or be withdrawn before surgery [1]. However, there is increasing evidence that people receiving prednisone up to 15 mg·day^{-1} can be safely operated on. Patients on mechanical ventilation are generally not accepted for lung transplantation. Although some patients have been successfully transplanted from a conventional ventilator, the perioperative mortality and morbidity is still high in this particular group. Lung transplantation is questionable in these patients due to donor shortage, long waiting lists and financial limitation.

Cystic fibrosis patients

Cystic fibrosis (CF) patients constitute the largest single group of people under 50 years of age dying each year in the United Kingdom and other countries from respiratory disease, but most transplant centres were for a long time reluctant to perform lung transplantation in these patients for fear of infection [3, 44]. In 1985, the first successful heart-lung transplants in CF patients were carried out in the UK. Today, more than 138 have been transplanted in the world, the majority in the UK. Early experience and more recent results have confirmed that heart-lung transplantation is a major therapeutic option for many patients with CF (fig. 1) [44, 48, 49] with a survival rate in this group similar to patients transplanted for other reasons [50, 51]. Indeed, actuarial survival of 78% at 1 year and 72% at 2 years has been reported by YACOUB et al. [50] in CF recipients, with an excellent quality of life in long-term survivors. However, particular problems inherent in CF, namely chronic bacterial chest infection, lung colonization by Aspergillus organisms; pneumothorax, chronic sinusitis, exocrine pancreatic insufficiency and malabsorption, diabetes mellitus, meconium ileus equivalent, liver disease and excess salt loss, require specific management before and after the transplant [52–55].

Although main sources of sepsis are removed by heart-lung or double lung transplantation, the trachea, sinuses and nasopharynx still remain a potential site of bacterial infection, mainly due to *Pseudomonas aeruginosa*, *Staphylococcus aureus* and *Haemophilus influenzae* [55]. Therefore, CF patients are treated with aggressive antibiotic treatment during the waiting period and routine post-transplant regimen includes IV anti-staphylococcus and anti-pseudomonas antibiotics together with aerosol colomycin [56, 57]. To date, there is no evidence that the incidence of early and late serious infectious complications are more frequent in CF recipients than in other groups of transplanted patients [3, 48, 50, 51].

Pneumothorax is a frequent complication of CF and an incidence of 19% has been reported in adults [52]. Treatment of pneumothorax should aim to avoid development of extensive pleural adhesions, since they represent a relative contraindication for subsequent heart-lung transplantation [44]. PENKETH et al. [52] treated small, first, asymptomatic pneumothorax conservatively and intercostal drainage was reserved for cases of complete collapse or symptomatic pneumothoraces. However, as a high mortality may be due to prolonged intercostal drainage, this procedure should not be carried out for more than a week [52]. In case of persistent air leak, limited surgical abrasion pleurodesis is the first line of treatment, while chemical pleurodesis, which is seldom effective in CF patients, is the second choice. Conventional surgical pleurectomy or talc pleurodesis may cause extensive pleural adhesions and should be avoided in potential lung allograft recipients.
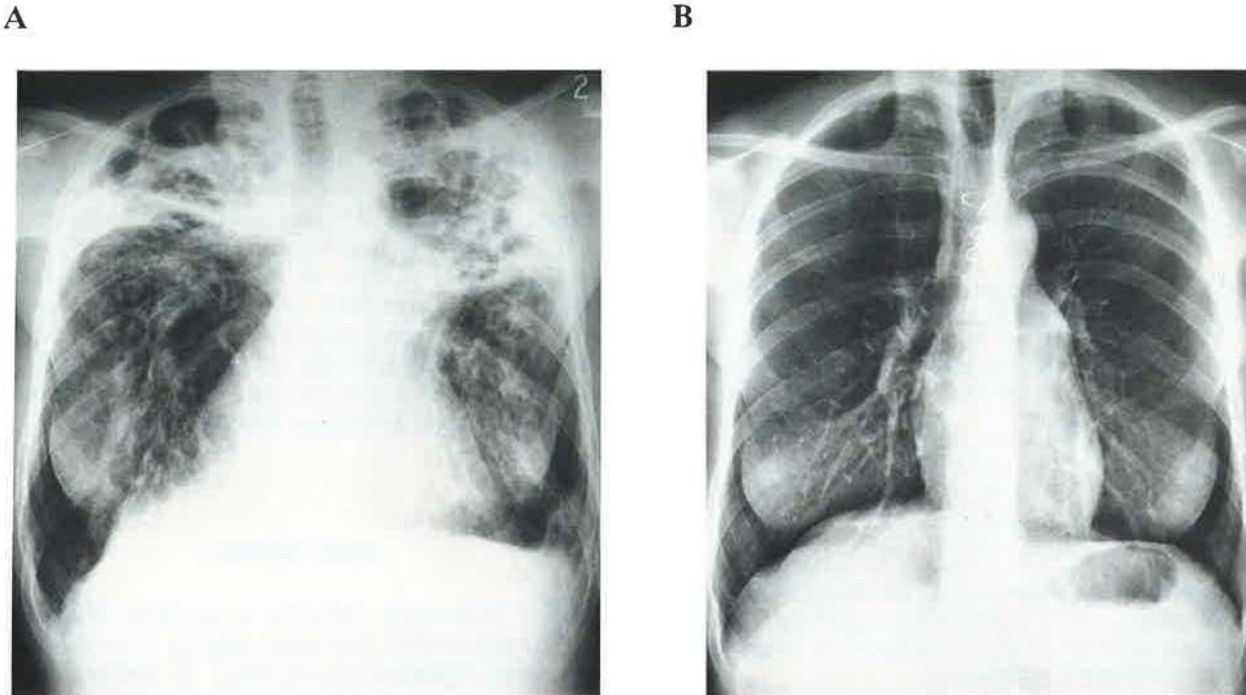
A

B

Fig. 1. – Chest radiographs from a young female with cystic fibrosis immediately before (A) and at one year following heart-lung transplantation (B).

Aspergillus fumigatus is often transiently cultured from the sputum in patients with CF [54, 55] and, because of the risk of severe postoperative opportunistic infection, aggressive treatment prior to transplantation is required [4, 50]. When sputum grows significant colonies of Aspergillus, patients are treated with aerosol natamycin and an oral antifungal agent, and transplantation is avoided until cultures are negative. Occurrence of allergic bronchopulmonary aspergillosis is likely to be a definitive contraindication, since severe corticosteroid dependent asthma usually coexists.

Insulin dependent diabetes mellitus without chronic or late complications is not a major contraindication [44, 49, 50]. Hepatic cirrhosis represents a contraindication. However, selected cases may benefit from heart-lung and liver transplantation [49, 50]

Donor selection and organ procurement

Development of pulmonary transplantation has been limited by the shortage of available donors and, in the early stages, by problems of distant organ procurement [58–62]. Although there are differences between centres, the following criteria for donor selection has been given: a) age <40 years; b) no history of significant cardiopulmonary disease; c) no pulmonary or systemic infections; d) normal or minor changes on chest radiograph; e) normal lung compliance and normal gas exchange is essential; f) no severe chest trauma; g) satisfactory cardiac function, normal electrocardiogram and minimal inotropic support; h) negative screening for hepatitis B and human immunodeficiency

virus [4, 59, 61–63]. When organs are available, donors and recipients are matched according to their ABO blood groups, chest sizes and cytomegalovirus (CMV) serological status [4, 62, 64, 65].

Several methods have been proposed for *ex vivo* preservation and distant organ procurements [4, 58, 60, 62, 66–68]. We employ a technique that involves cooling the donor using a portable cardiopulmonary bypass machine before harvesting the organs. In this way, heart and lungs from donors as far as 1500 miles from Harefield, with ischaemic times of up to 5 h, have been successfully implanted [4].

Immunosuppression regimens

Cyclosporin A, with its selective and reversible inhibition of immunocompetent T-lymphocytes, is considered today as the first-line treatment to suppress allograft rejection [69]. Cyclosporin is absorbed in the upper small intestine, metabolized by the liver and its metabolites are mainly eliminated *via* the bile [70]. Cyclosporin's mean bioavailability is about 30% but this can be much less in those recipients with gastrointestinal disorders (*e.g.* patients with CF) [70, 71]. Since there are marked individual and interindividual differences in oral absorption and clearance rates, monitoring of cyclosporin concentration is imperative to minimize toxicity and to optimize immunosuppression [70, 72]. Nephrotoxicity represents the main side effect of cyclosporin therapy and acute impairment of renal function can occur in the postoperative period [73–77]. However, spontaneous recovery is usually

achieved by withholding or reducing temporarily the cyclosporin administration [78]. Long-term treatment with cyclosporin may also lead to chronic nephropathy. Indeed, reduced glomerular filtration and renal plasma flow together with tubulointerstitial injury and focal glomerular sclerosis have been demonstrated [75]. Hypertension is another frequent problem in cyclosporin-treated recipients [76].

Table 2. – Immunosuppressive protocol variations in different heart-lung and lung transplant centres

Transplant unit	Perioperative protocols	Maintenance protocols
Harefield	C, A, M, ATG	C, A
Papworth	C, A, M, ATG	C, A
Pittsburgh	C, A, M, ATG	C, P
Stanford	C, A, M, OKT3	C, A, P
Toronto	C, A, ALG	C, A, P

C: cyclosporin; A: azathioprine; M: methylprednisolone; P: prednisone; ATG: antithymocyte globulin; OKT3: monoclonal antibody to the T3 receptor on lymphocytes; ALG: antilymphocyte globulin.

Nifedipine is usually effective and this drug might be beneficial in preserving renal function [79]. Other complications include hyperkalaemia, hepatotoxicity, gingival hyperplasia, hirsutism and convulsions [76, 80, 81]. Apart from cyclosporin, the major forms of immunosuppression include azathioprine, corticosteroids, antithymocyte globulin (ATG), antilymphocyte globulin (ALG) and monoclonal antibody to the T3 receptor on lymphocytes (OKT3) [80, 82–86]. The main side-effects of these drugs have been reviewed elsewhere [82]. Immunosuppressive regimens vary from one transplant unit to another and differences are summarized in table 2. Details of immunosuppressive protocol used at Harefield Hospital and the Royal Brompton Hospital are given in table 3.

Acute rejection

Acute pulmonary rejection is common following lung transplantation and rates ranging from 50–87% have been reported [7, 11, 87]. It appears more

Table 3. – Current immunosuppression regimen for heart-lung and lung transplantation at Harefield and the Royal Brompton Hospitals

Time of administration	Regimen	Notes
Preoperative	C: 2–10 mg·kg^{-1} P.O.	The dose of cyclosporin is reduced if preoperative serum creatinine ranges between 120 and 170 μmol·l^{-1}. No cyclosporin is given if preoperative serum creatinine is above 170 μmol·l^{-1}.
	A: 2 mg·kg^{-1} P.O.	Providing normal white blood cell count and no evidence of significant impairment of liver function.
Intraoperative	M: 1000 mg i.v.	On reperfusion.
Postoperative	C: 4–20 mg·kg^{-1}·day^{-1} P.O.	During the first 24–48 hrs and especially in cystic fibrosis patients, cyclosporin is often given i.v. (2 mg·kg^{-1}·day^{-1}). Blood level: 500 ng·ml^{-1} in the first month*. The dose of cyclosporin is reduced for mild impairment of renal function. If serum creatinine level is >200 μmol·l^{-1}, prednisone 1 mg·kg^{-1}·day^{-1}, progressively reduced to 0.2 mg·kg^{-1}·day^{-1}, is used instead of cyclosporin.
	A: 1–2 mg·kg^{-1}·day^{-1} P.O.	Adjusted to keep white blood cells >4,000·mm^{-3}.
	M: 125 mg i.v. q12h	Methylprednisolone is stopped as soon as cyclosporin blood level ≥300 ng·ml^{-1}*.
	ATG: 100 mg i.v. every other day during the 10 first postoperative days.	
Maintenance	C: 4–20 mg·kg^{-1}·day^{-1} P.O.	Blood level: 250–350 ng·ml^{-1}*. Renal dysfunction: same rule as above
	A: 1–2 mg·kg^{-1}·day^{-1} P.O.	Adjusted to keep white blood cells >4,000·mm^{-3}.
Acute rejection	M: 1000 mg daily × 3 doses	
	P: 0.5–1 mg·kg^{-1}·day^{-1} P.O.	To complement methylprednisolone in case of moderate or severe rejection. The dose is reduced according to clinical outcome.
	ATG or OKT3:	May be considered for refractory rejection.

For abbreviations see legend to Fig. 2. P.O: per os. *: cyclosporin levels are assessed by monoclonal antibody on whole blood.

frequently during the first three months after surgery but rejection episodes may arise at any time during follow-up [4, 7, 11]. Cough, breathlessness and a low grade of pyrexia are common and auscultation may reveal wheezes with late inspiratory crackles. In a series reported by PENKETH *et al.* [87], only 15% of patients with rejection were symptom free.

Laboratory lung function testing and daily home spirometry are valuable in post-transplant assessment and the occurrence of rejection or infection should always be considered when forced expiratory volume in one second (FEV_1) or forced vital capacity (FVC) fall by 10% from the usual values (fig. 2) [88–91].
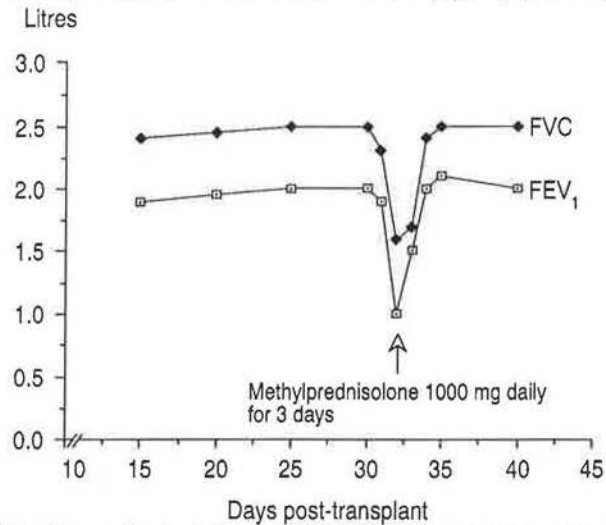

Fig. 2. – Typical changes of the forced expiratory volume in one second (FEV_1) and forced vital capacity (FVC) during an episode of acute pulmonary rejection in a cystic fibrosis heart-lung transplant recipient. The figure shows a rapid improvement of the spirometric values following the treatment of methylprednisolone (arrow).

On the other hand, allograft lung rejection may also develop without impairment of respiratory functional parameters [92] and temporary irrelevant fluctuation in FEV_1 can sometimes occur [89].

Abnormalities in the chest radiograph may also reveal acute rejection (fig. 3) [4, 93]. For example, MILLET *et al.* [93] found radiographic changes in 74% of rejection episodes occurring during the first postoperative month, while abnormalities were only seen in 23% of cases arising later than one month after surgery. Lung changes may range from interstitial shadowing to airspace consolidation [4, 93, 94]. Pleural effusion, alone or in association with lung changes, may also be due to rejection [93]. Radiographic abnormalities, when present, are not specific and do not allow distinction between rejection and infection. However, they offer a useful indication in guiding transbronchial biopsy and bronchoalveolar lavage.

Attempts to use bronchoalveolar lavage cell counts in diagnosing rejection *versus* bacterial or viral infection have recently been made [95–99]. To date, the precise clinical significance of normal or abnormal bronchoalveolar cell profiles is still unclear.

By contrast, the role of transbronchial lung biopsies is well defined and high sensitivity and specificity in detecting rejection are provided by using this technique [100–104]. Satisfactory results have been obtained by taking 3–4 biopsies on each occasion, either from areas of pulmonary shadowing or from a lower lobe in the case of normal radiology [100]. It has recently been suggested that biopsy of all lobes of one lung should be undertaken to optimize sensitivity [105–107]. The histological features of rejection consist of dense perivascular mononuclear infiltrates with minimal extension into alveolar septa (fig. 4) [100, 108, 109].
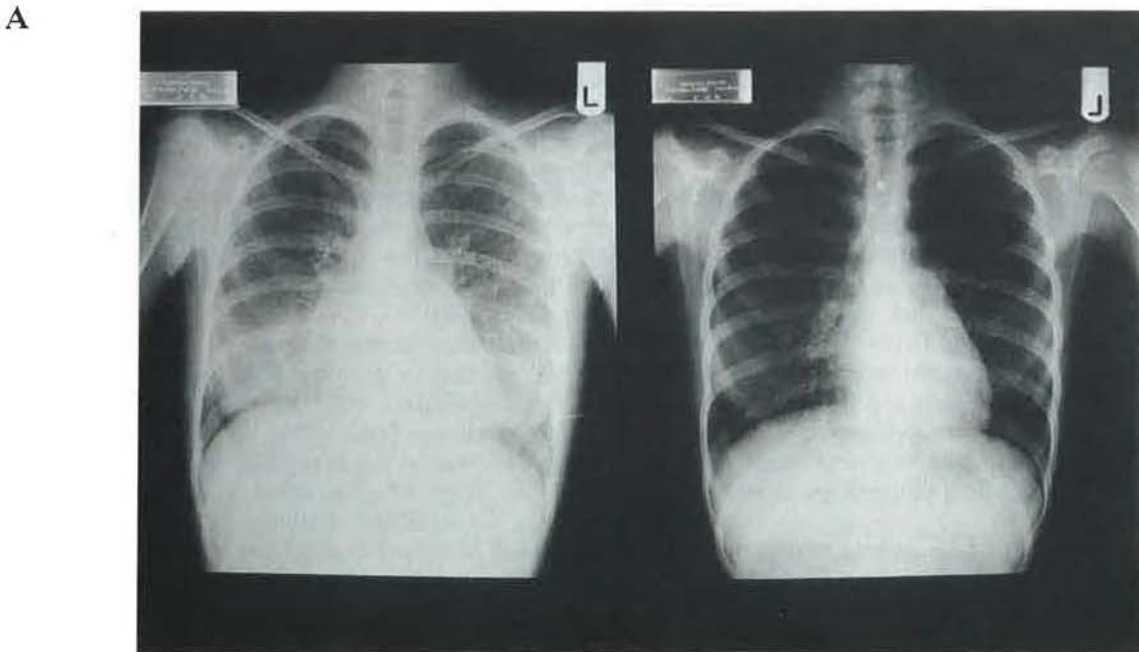
A   **B**

Fig. 3. – Chest radiographs from the same patient as in figure 2 before (A) and after (B) treatment with IV methylprednisolone.
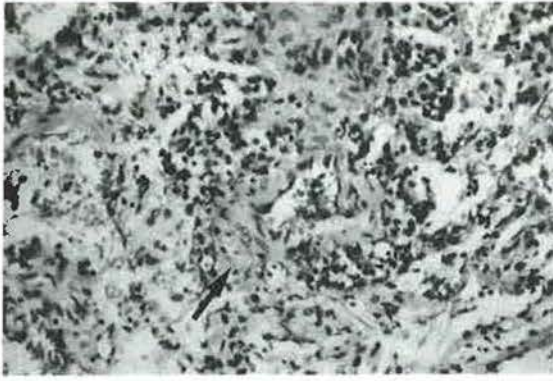
Fig. 4. – Transbronchial biopsy (stained with Haematoxylin and Eosin) from a patient with acute pulmonary rejection demonstrating perivascular cuffing by mononuclear cells (arrow).

According to experimental findings [1] and early clinical experience [110], it was believed that the heart and lungs would reject synchronously and that endomyocardial biopsy would enable diagnosis of both cardiac and pulmonary rejection in heart-lung transplant recipients. Further investigations have, however, shown that rejection of the lung frequently occurs without synchronous cardiac rejection, and that isolated cardiac rejection is rare [11, 87, 111–113]. Therefore, the abandonment of routine endomyocardial biopsy in heart-lung recipients has been suggested [7, 87]. Acute rejection is treated with a transitory augmentation of immunosuppression, leading frequently to rapid clinical improvement (table 3).

Obliterative bronchiolitis

In the early Stanford experience [6], high morbidity and mortality rates in long-term survivors with heart-lung transplants were related to obliterative bronchiolitis, a disease characterized by obstruction and destruction of pulmonary bronchioles [114]. This complication has also been reported after single lung transplantation [115].

The precise pathogenesis of obliterative bronchiolitis is unknown, but it may represent a form of rejection, related to increased expression of class I and II major histocompatibility complex antigens on bronchiolar and alveolar epithelium and vascular endothelium in the transplanted lung [116–119]. Ischaemic necrosis due to lack of bronchial arterial supply may also play a role. Early diagnosis and treatment of pulmonary rejection as well as optimal maintenance immunosuppression should lead to improvement in the long-term prognosis after lung allograft transplantation [87, 114, 120].

First manifestations may arise several months to 1–2 yrs after surgery and the progression of the disease can be rapid in approximately 50% of those affected [121, 122]. Clinically, obliterative bronchiolitis is characterized by dyspnoea, cough with or without sputum, chest tightness or wheezing [90, 120, 121, 123].

Examination may reveal persistent tachypnoea and bilateral basal inspiratory crackles with occasional rhonchi [90, 120]. Pulmonary function testing reveals obstructive ventilatory impairment with progressive decrease in flow rates to very low values (fig. 5), and little or slight improvement is produced by bronchodilators [90, 120, 121, 123]. The increasing airflow obstruction leads to arterial hypoxaemia with concomitant hypocapnia rather than CO_2 retention [121]. The chest radiograph may be normal or may demonstrate hyperinflated lung fields or evidence of basal peribronchial infiltration [121].
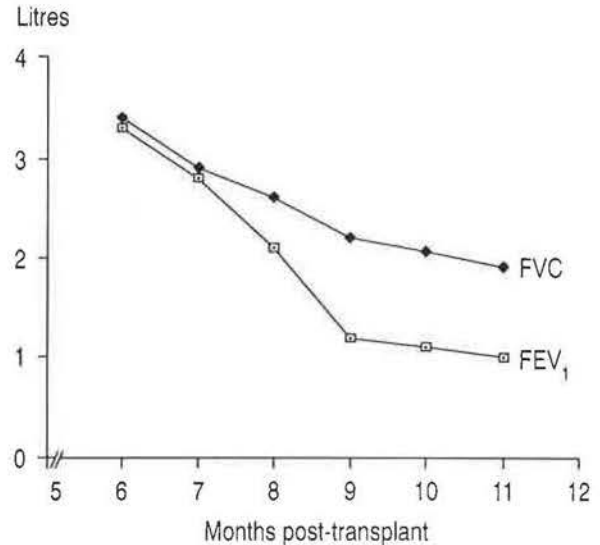

Fig. 5. – Progressive decline of the forced expiratory volume in one second (FEV_1) and forced vital capacity (FVC) with time in a heart-lung transplant recipient with obliterative bronchiolitis. The patient did not respond to augmented immunosuppression.

The diagnosis of obliterative bronchiolitis can be confirmed by transbronchial biopsy and in a small series reported by YOUSEM et al. [123], a clinical suspicion of obliterative bronchiolitis was confirmed in 66% of cases by this method, reaching 100% when transbronchial biopsy was repeated. Moreover, in instances where no terminal or respiratory bronchioles are present for histological evaluation, ongoing obliterative bronchiolitis should be suspected when chronic inflammation of the bronchi is present [124]. Open lung biopsy is rarely necessary to confirm this diagnosis [101, 108].

Morphological changes related to obliterative bronchiolitis are usually panlobar with patchy involvement, and the histological findings vary according to the stage of evolution [109, 125]. In the earliest phases, usually observed at transbronchial biopsy, the changes consist of plugs of granulation tissue located in the lumen of terminal and respiratory bronchioles, associated with ulcerated bronchiolar epithelium and submucosal infiltration with chronic inflammatory cells [121, 123]. Later, a scaring process develops and a wide range of luminal impairment can be observed. A common feature is a thickened fibrotic submucosa, resulting in reduced luminal diameter and a rigid

bronchiole. In the most severe cases, the bronchiolar lumen may be entirely occluded by dense scar tissue (fig. 6) [109, 125].

Although increased immunosuppression arrests or prevents progression in approximately 50% of patients, functional impairment related to obliterative bronchiolitis is often inexorably progressive [120, 121, 126, 127]. The prognosis remains consequently poor, and patients either die or are severely limited by dyspnoea [120, 121]. Sometimes, retransplantation is the only chance of survival [121]. Recent reports suggest nevertheless that the incidence of obliterative bronchiolitis may be decreased by a close monitoring of lung function and an early diagnosis of pulmonary rejection by transbronchial biopsy [87, 123].
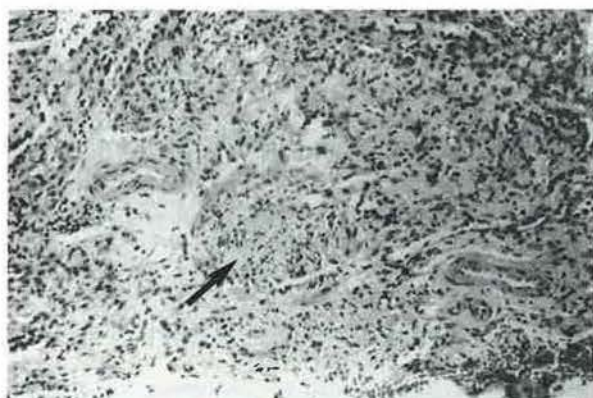

Fig. 6. – Transbronchial biopsy (stained with Haematoxylin and Eosin) from a patient with obliterative bronchiolitis. Note obliteration of terminal bronchiole by lymphoid and fibrous tissue (arrow). An interstitial mononuclear cell infiltration is also present.

Infectious complications

Infectious complications, especially affecting the transplanted lung, occur frequently after transplantation and are an important cause of morbidity and mortality [128–130]. Incidence of infection as high as 86% was reported in two early series [128, 129] and 75% of all deaths have been related to infection in the overall Pittsburgh experience [130]. In addition to immunosuppression, many other factors affecting lung defence mechanisms can explain this high tendency for developing infections. In the early postoperative period, ischaemic injury, impaired pulmonary drainage and interrupted lymphatic drainage may predispose to bacterial pulmonary infection [128, 130–132]. Later, increase in immunosuppression to treat acute rejection, structural lung changes related to chronic rejection and obliterative bronchiolitis, and bacterial airway colonization are some of the factors which may predispose to infection (table 4) [90, 128, 129].

During infection, patients are usually symptomatic, and fever is the main symptom, followed by dyspnoea and cough [87, 100]. Just as in rejection, infection can cause an impairment of spirometric values, and both diagnoses must be considered if FEV_1 or FVC fall by 10% of the usual values [88–90].

Table 4. – Main pathogens in heart-lung transplant infections

Bacterial	Pseudomonas sp.
	Staphylococcus aureus
	Hemophilus influenzae
	Pneumococcus
	Enterobacteriaceae
Viral	Cytomegalovirus
	Epstein-Barr virus
	Herpes simplex virus
Protozoal	Pneumocystis carinii
	Toxoplasma gondii
Fungal	Aspergillus sp.
	Candida albicans
	Cryptococcus neoformans

Chest radiographs are often abnormal, but radiographic changes can be similar to those seen in rejection, and again distinction between rejection and infection can rarely be made in this way [93].

When suspicion of infection arises, lung function testing and chest radiographs should be performed together with sputum microbiology and blood cultures. However, sputum and even transtracheal aspiration cultures often grow multiple potential pathogens and the interpretation of these microbiological results is often problematic [128, 129]. Thus, if these investigations are inconclusive, bronchoalveolar lavage and transbronchial biopsies should be carried out quickly, since the combination of these two techniques provides a high diagnostic yield in diagnosing pulmonary infection in immunodeficient patients and in lung transplant recipients [101, 130, 133–139].

Bacterial infections

The transplanted lung is particularly sensitive to bacterial infection and a prevalence of bacterial pneumonia greater than 60% has been reported [128, 130]. Bacterial pneumonia can occur at any time after transplantation, but is common in the early postoperative period [128, 130]. Pseudomonas sp., Staphylococcus aureus, Hemophilus influenzae, S. pneumoniae and Enterobacteriaceae are the main pathogens isolated, but infection related to Mycoplasma hominis, Legionella pneumophila, and typical or atypical Mycobacteria can sometimes occur [100, 128–130, 140].

Cytomegalovirus infections

CMV infection, which frequently occurs during the first months after surgery, may lead to a high morbidity and mortality in lung allograft recipients [141–146]. For clinical convenience, it is worth distinguishing asymptomatic from symptomatic CMV infection with or without CMV pneumonitis [130, 142]. Fever, myalgias, malaise, abdominal discomfort as well as leucopenia, thrombocytopenia, atypical

lymphocytosis and hepatitis are the usual clinical manifestations of a symptomatic CMV infection [130, 141, 142]. This syndrome is often associated with CMV pneumonitis in lung allograft recipients [130]. On the other hand, isolation of CMV in bronchoalveolar lavage (BAL) is not uncommon in case of asymptomatic CMV infection without evidence of CMV pneumonitis.

A CMV seronegative recipient before transplantation, can acquire a primary CMV infection by receiving an organ from a CMV antibody-positive donor or *via* virus-containing blood products [142–146]. In patients who are CMV antibody-positive before the transplant, CMV infection can be due to reactivation of the recipient's endogenous strain or, in the case of CMV antibody-positive donor, to reinfection with a different donor's strain [145, 147–149].

In the Papworth experience, the reported incidence of CMV infection was 78% in antibody-negative heart-lung transplant recipients receiving organs from CMV antibody-positive donors [145]. This group of patients as well as a similar group transplanted in Pittsburgh, were then at high risk of developing a life-threatening or fatal CMV disease, frequently related to pneumonia [130, 145, 146]. Conversely, in the Papworth series, CMV antibody-negative recipients experienced primary CMV infection in only 20% of cases by receiving organs from a CMV antibody-negative donor and CMV infection acquired from blood or blood products in this group, was usually less severe [145]. A further reduction of CMV infection in seronegative recipients can also be achieved by using exclusively seronegative blood products in addition to seronegative organs [130, 146].

In CMV antibody-positive recipients before the transplant, incidence of CMV reactivation or reinfection is usually high, but it seems that the outcome can be influenced by the donor serological status [130, 145, 146]. Indeed, in the Papworth study [145], all CMV antibody-positive heart-lung transplant recipients experienced reactivation or reinfection by receiving organs from a CMV antibody-positive donor, while the incidence of CMV infection fell to 57% by receiving organs from a CMV antibody-negative donor. Furthermore, the severity of CMV disease was less in this former group. In the Pittsburgh series, 95% of all seropositive recipients developed serological evidence of infection and among these patients 32% developed a CMV disease, frequently including pneumonia [146].

CMV infection can be assessed serologically by using the complement fixation test (CFT), competitive enzyme-linked immunosorbent assay (ELISA) and the detection of specific antibody to CMV (IgM and IgG) [145, 150]. In patients free of detectable CMV antibody before transplantation, primary CMV infection is diagnosed when a significant rise in CMV antibody is demonstrated in blood samples taken after transplantation (≥four-fold rise by CFT, >50% inhibition in competitive ELISA) [142–145]. On the other hand, CMV reactivation or reinfection is established when a significant rise in CMV antibody occurs (≥four-fold

rise by CFT) in patients whose serum already contained detectable CMV antibody before transplantation [142–145].

To assess a CMV infection or a CMV syndrome, serology is usually complemented by viral culture in blood, urine, saliva, while cytological and histological examination of bronchoalveolar lavage and transbronchial lung biopsy are essential tools in diagnosing CMV pneumonitis [101, 142, 151–157]. Early studies showed that CMV isolations from saliva and urine were not very sensitive and specific in diagnosing a CMV syndrome while a positive blood culture correlated better [142, 151].

CMV culture carried out in BAL, was found to be highly sensitive in detecting CMV pneumonitis [153, 154, 156]. However, the lack of specificity of this method as well as the long interval necessary to detect the characteristic CMV cytopathic effect, make BAL culture insufficient in the clinical setting [152, 153, 155, 157, 158]. On the other hand, cytological examination of lung lavage cells, looking for typical nuclear and cytoplasmic viral inclusions, was shown to be very specific but with a poor sensitivity [153, 154]. Thus, according to the respective sensitivity and specificity of cytological examination and CMV culture of BAL, CMV pneumonitis can reasonably be assessed by a positive culture and a positive cytology, whereas this diagnosis is unlikely when the culture is negative [153].

Other techniques, related to fluorescent monoclonal antibodies against the early CMV antigen (DEAFF test – detection of early antigen fluorescent foci), DNA hybridization and centrifugation culture have been developed to ensure a rapid, sensitive and specific detection of CMV [153–156, 158–161]. For example, PARADIS *et al.* [153], demonstrated a high negative predictive value in detecting CMV pneumonitis by using CMV-specific monoclonal antibodies on cells recovered by bronchoalveolar lavage. Thus, similarly to negative viral culture, CMV pneumonitis is improbable when viral antigen in lung cells are not detected by this technique. However, clinical suspicion of CMV pneumonitis must often be confirmed histologically by taking biopsy samples transbronchially [157]. The histological features are related to diffuse alveolitis frequently with diagnostic viral inclusions [108].

The high morbidity and mortality associated with CMV disease and particularly CMV pneumonitis, might be favourably affected by the use of ganciclovir [162]. The clinical efficacy of this drug has been documented in other immunocompromised patients [163–165] but CMV strains resistant to ganciclovir have already arisen [166]. A combination of ganciclovir and CMV immune globulin has also been suggested to treat severe CMV infection and CMV pneumonia in bone marrow and liver transplants [167–169]. Moreover, as shown in renal, heart and bone marrow transplant recipients, prophylactic use of CMV immune globulin might be useful in lung allograft recipients with high risk of developing CMV disease [170–176]. In pulmonary allograft recipients, treatment of CMV disease and CMV

pneumonia is currently based on clinical experience. Ganciclovir with or without CMV immune globulin are currently used and therapeutic successes have been reported [130, 144, 145]. The major side effect of ganciclovir is a reversible and dose-dependent neutropenia [164, 165]. Adverse reactions related to treatment with CMV immune globulin seem to be rare [170, 175, 176].

The policy at Harefield Hospital, is to use ganciclovir 5 mg·Kg⁻¹ i.v. twice a day for 14–21 days. In cases of severe CMV disease or CMV pneumonitis, this treatment is sometimes empirically complemented by CMV immune globulin, but clinical trials are currently in progress.

Other herpesvirus infections

Major problems related to herpes simplex virus (HSV) and Epstein-Barr virus (EBV) are not uncommon in lung allograft recipients [109, 128, 129, 177, 178]. In the Papworth series, for example, symptomatic HSV infection developed in 18% of 51 heart-lung transplant recipients [178]. In this study, all patients were HSV seropositive before the transplant and the clinical manifestations were related to mucocutaneous lesions of the mouth, throat, and nose, frequently combined with pneumonia [178]. However, involvement of the skin, viscera and brain may occur [179] and disseminated HSV infection in seronegative, pretransplant, solid organ recipients has also been reported [180]. Serology as well as viral culture of mucocutaneous lesions, bronchoalveolar lavage and lung tissue are important tools for the diagnosis of HSV infection. Furthermore, in cases of HSV pneumonia, histological evidence of necrotizing or haemorrhagic pneumonia with characteristic eosinophilic intranuclear inclusion should be seen in the lung specimens [178, 181]. Acyclovir is the treatment of choice in cases of symptomatic HSV infection [178, 179, 182]. Moreover, since HSV infection frequently develops within the first postoperative months [178] and since effective prophylaxis against HSV can be achieved by acyclovir [183], prophylactic acyclovir 200 mg four times daily can be recommended for every lung allograft recipient during the first three months after surgery. A similar regimen should also be considered in cases where immunosuppression is augmented [178].

In a study carried out by WREGHITT et al. [177], in 156 heart and heart-lung transplant recipients, primary EBV infection has been diagnosed in 8% and secondary EBV infection in 24%. Similarly, in the Pittsburgh series, primary EBV infection has occurred in 12% of 60 lung allograft recipients [130]. EBV infection is frequently asymptomatic, although a mononucleosis syndrome sometimes develops [130, 177]. However, a strong association exists between EBV infection and post-transplant lymphoproliferative disorders [184] and an incidence of EBV-associated lymphoproliferative disease of up to 7% has been reported in heart-lung transplant recipients [185]. Fever,

enlargement of head and neck lymph nodes, tonsillitis, sore throat as well as abdominal complaints related to gastrointestinal mass lesions and liver and renal dysfunction are the most frequent signs and symptoms [184]. Lymphoproliferative disorders primarily located in the lung allograft can also occur [186]. Where the lymphoproliferative disorder is related to EBV, reduction of immunosuppression and particularly cyclosporin together with high dose acyclovir is required and complete regression of the tumour usually occurs [184, 185, 187].

Protozoal and fungal infections

Serial bronchoalveolar lavage performed in lung allograft recipients who did not receive effective antibiotic prophylaxis has revealed a high incidence of *Pneumocystis carinii* infection [138]. Signs and symptoms of pneumonia can be present, although patients frequently are asymptomatic with a normal chest radiograph or complain about upper respiratory tract symptoms [130, 138]. Prophylactic therapy with trimethoprim-sulfamethoxazole is effective and occurrence of *Pneumocystis carinii* infection is now rare in treated patients. As adverse reactions are frequent with a daily therapy [138], interval prophylactic regimens are currently prescribed, but with large differences from one centre to another [130, 188]. The Harefield regimen consists of trimethoprim-sulfamethoxazole 960 mg twice daily every third day. In those patients intolerant of trimethoprim-sulfamethoxazole, aerosol pentamidine 600 mg is given twice a month.

Transplant recipients may experience reactivation of latent *Toxoplasma gondii* (*T gondii*) infection or may acquire primary *T gondii* infection from seropositive donor organs [189–193]. In a serological study carried out by WREGHITT et al. [193], on 217 heart and 33 heart-lung patients evidence of *T gondii* recrudescence has been found in 2% and primary *T gondii* infection in 2.4%. Clinical manifestations are mainly neurological, although myocarditis, pneumonitis or disseminated lesions can also arise [189, 192]. The extent of the lesions in the central nervous system is variable and histological findings usually consist of granulomatous lesions often accompanied by necrosis of the parenchyma [194]. Single or multiple hypo-dense lesions with central noncalcified hyper-dense regions are characteristic on brain computerised tomography [195]. Diagnosis can be made by using serological tests [191, 196, 197] or by assessing the presence of the Toxoplasma parasites on biopsy specimens [192–194]. Pyrimethamine in combination with sulphonamides is the current regimen to treat Toxoplasmosis [198]. Furthermore, prophylaxis with pyrimethamine seems to be effective in preventing severe infection in *T gondii* antibody negative transplant recipients receiving organs from *T gondii* antibody positive donors [193].

Most fungal infections have been related to *Candida albicans* although infections due to Aspergillus species or *Cryptococcus neoformans* have also been reported

[109, 128–130]. The spectrum of clinical manifestations is wide and may range from tracheal colonization to tracheal or aortic anastomotic infections, pneumonitis, mediastinitis or disseminated disease. Treatment of severe cases is usually started with intravenous amphotericin B, in spite of the risk of renal failure in cyclosporin-treated patients [109, 199]. Itraconazole and ketoconazole have also been used in a few cases, but careful monitoring of cyclosporin levels is necessary to avoid renal function impairment [200, 201].

Pulmonary function and exercise tolerance

Heart-lung transplant recipients who survive the first six postoperative months can expect a substantial improvement in lung function, more than 80% of them achieving a normal FEV_1 at 12 months [50, 202, 203]. Furthermore, providing the allografts remain free of complications, long-term survivors may have well preserved lung function [6, 204]. In the same way normal lung function can be obtained by double-lung transplantation [39, 202]. After single lung transplantation, a persistent restrictive ventilatory defect has been reported in patients transplanted for endstage restrictive lung disease, whereas recipients with obstructive lung disease may remain with an obstructive ventilatory defect [202]. At rest, either normal or near-normal blood gases can be obtained by single, double and heart-lung transplantation [31, 39, 50, 202]. During exercise, the maximum workload after heart-lung transplantation is lower than in normal subjects, but is similar to that after cardiac transplantation [205]. Heart-lung transplant recipients show evidence of an altered pattern of breathing during exercise [205, 206] probably due to pulmonary denervation. Single lung and double-lung transplantation also improve exercise performance. However, maximum oxygen consumption remains below normal values [202, 207].

Conclusion

The development of surgical techniques together with immunosuppression with cyclosporin have allowed lung transplantation to become an effective treatment in carefully selected patients with pulmonary vascular disease and end stage lung disease. After successful transplantation, functional results are excellent and recipients may achieve a good quality of life. However, scarcity of suitable donors is an important limiting factor, and opportunistic infection, rejection and obliterative bronchiolitis are still a major cause of morbidity and mortality. Thus, further research is urgently required into prevention and treatment of early and late post-transplant complications.

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