Management of cystic fibrosis before and after lung transplantation

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J R Soc Med 1997;**90**(Suppl. 31):47–58 SECTION OF PAEDIATRICS , 20 NOVEMBER 1996

INTRODUCTION

Increasingly sophisticated medical therapy has altered the survival of patients with cystic fibrosis (CF) such that, in general CF patients can expect a life span into their early adulthood. The major cause of death persists in the form of pulmonary sepsis and respiratory failure. The surgical treatment of lung transplantation has evolved to a level where patients can be offered extended survival following isolated lung transplantation and heart/lung transplantation[1]. The availability of transplantation has profoundly altered the emphasis of care for CF patients. Care was previously directed at ensuring that the patient died in comfort when medical treatment had failed. Now, when medical treatment is perceived as reaching a phase where it is likely to fail, a patient may be offered the option of transplantation. This strategy has created the need for skills aimed at, selecting patients for transplantation, keeping the patient alive in optimal clinical condition and allowing the patient appropriate palliative care if a graft is not forthcoming. This article outlines some of the issues of clinical management relating to CF patients before and after lung transplantation.

PATIENT SELECTION FOR TRANSPLANTATION

CF patients presented with the eventuality of transplantation require an insight into the survival following transplantation. The international actuarial one year survival for adult heart/lung transplantation is approximately 60% with a 10 year survival of 25%[2]. The international one year survival for adult double sequential lung transplantation is 67% and the 42 month survival is 47%[2]. The difference in follow up between the two procedures reflects upon the difference in survival rates quoted. Heart/lung transplantation figures include the early experience in transplantation, while double sequential lung transplantation is occurring in centres with experience gained from the early heart/lung transplant 'era', thereby conferring an apparent survival advantage.

Discussion regarding transplantation focuses the patient's attention on their expected survival without lung transplantation. This often evokes denial of the severity of their status. Such denial may manifest as a request to be placed on a provisional list for transplantation. However, some patients' attitude can change dramatically when they perceive the severity of their disease, having previously considered themselves to be in relatively good health[3]. Centres vary in their application of the concept of provisional listing. Applying a provisional status to a patient is frought with problems and risks diminishing the window required to achieve a graft for the patient. Currently the waiting period for transplantation is in the region of 24 months with between 30–50% of patients dying on the waiting list. What in essence provisional listing tries to evoke is close liaison and effective communication between referring cystic fibrosis centre and the transplant programme. In the UK on the basis of regionalization of transplantation (specific programmes responsible for specific regions of the country) and local referral patterns, such communication can be readily achieved in the context of predicting patient survival and updating the transplant programmme on the clinical status of the future potential transplant recipient. Kerem *et al.* have produced epidemiological data which suggests that 50% of patients with an FEV_1 of less than 30% will die within two years and should be referred for transplantation[4]. However, it can be difficult to predict patient survival at an individual level based upon poor respiratory function. Furthermore, some patients can survive with severely impaired pulmonary function but with a good quality of life. Although CF patients at the time of dying from respiratory failure usually have an FEV_1 $<30\%$, predicting decline in respiratory function for the individual patient with severe disease is imprecise. In another study, patients two years prior to death had an average FEV_1 of 38% (range 20–80%)[5]. Therefore other surrogate markers of disease progression including weight loss, repeated hospital admissions, reduced functional capacity, compliment the physiological assessment of decline.

Colonizing organisms are also factors taken into account when assessing rate of decline. The progression of pulmonary sepsis with *Pseudomonas aeruginosa* (*P. aeruginosa*) is relatively slow. This slow pace usually leaves sufficient time to list a patient for transplantation who is becoming unresponsive to multidisciplinary treatment. Occasionally pulmonary sepsis

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will progress rapidly and this is more commonly associated with infection with *Burkholderia cepacia* (*B. cepacia*). Rarely, CF patients who have been chronically infected with *B. cepacia*, progress rapidly to a necrotizing pneumonitis and death following a viral infection[6]. Therefore the data presented by Kerem *et al.* can be used as a guide for appropriate timing of referral for transplantation but regular and effective communication between CF centre and the transplant programme is the best strategy.

Contraindications

At the inception of lung transplantation there was a comprehensive list of contraindications. The success of transplantation based on 'hard earned experience' has allowed many prior contraindications to be dismissed, notably the anxieties regarding the use of oral corticosteroids and diabetes mellitus. Many factors previously considered to be contraindications can now be addressed and resolved for the benefit of the patient. This is most apparent with respect to coexisting major system disease. If significant liver disease or renal disease exist a patient can be evaluated in the context of multiorgan transplantation[7]. When a CF patient has portal hypertension as demonstrated by the presence of varices, the only option is triple organ transplantation. However, a significiant number of CF adults will have palpable hepatosplenomegaly with normal liver function tests. Assessing the severity of liver disease when ascites and portal hypertension are absent can be difficult. However in such circumstances it is unusual for hepatic decompensation to occur during organ transplantation.

Other factors may be considered to be 'relative' contraindications based on clinical experience. These include colonization with *B. cepacia* and *Aspergillus fumigatus* (*A. fumigatus*), poor nutritional status, severe atopy, and non compliance with absent or poor family support. The objective and accurate assessment of compliance is frought with difficulty. Compliance to complex drug regimens following transplantation does not normally pose a CF patient difficulty. However, patients who are informed in depth regarding CF and have close ties to the CF multidisciplinary team can be reluctant to adopt a different discipline with respect to the issues of transplantation. The most important of these post transplant deciplines is early self-referral in the event of an evolving clinical problem. To preclude a patient on the basis of non compliance or to list a patient with questionable compliance requires careful consultation between the transplant programme and the referral centre. Absolute contraindications include active or uncontrolled psychotic illness, mechanical invasive ventilatory support, infection with atypical mycobacterium and recent neoplasia (Table 1).

Table 1 **Absolute and relative contraindications to transplantation**

Relative contraindications	*Absolute contraindications*
B. cepacia colonization	Invasive mechanical ventilation
Non-compliance	Psychotic illness
Liver disease	Atypical mycobacterium
Renal dysfunction	*B. cepacia* related septicaemia
Aspergillus	Recent neoplasia
Poor nutritional status	
Methicillin-resistant *Staphylococcus aureus*	

MANAGEMENT ISSUES IN THE CONTEXT OF TRANSPLANTATION

Nutritional status

Adequate nutrition is one of the most significant prognostic factors influencing survival in cystic fibrosis[8]. A major cause of weight loss is energy expenditure related to pulmonary sepsis and declining respiratory function. Inevitably the increased work of breathing associated with frequent infective exacerbations also increase energy expenditure[9]. During the pre-transplant period it is important to maintain adequate nutritional status. Those patients who undergo lung transplantation with body weight below 80% of predicted for their height have a reduced survival following transplantation[10].

At the Wythenshawe Transplant programme we recommend that all patients should have a feeding gastrostemy inserted when they have been listed for transplantation. The insertion of a feeding gastrostomy can provide adequate nutrition and preserves body weight prior to transplantation. The commonest problem with supplemental feeding is gastric distension and vomiting. If the rate of delivery exceeds the rate of gastric emptying, the patient awakes with a distended stomach and vomits. This situation can be avoided by either reducing the volume or the rate of delivery of the feed and stopping the feed two hours before the patient wakes. The prescription of prokinetic drugs (e.g. cisapride) may help. Feeds with a high carbohydrate content may increase carbon dioxide production and may precipitate type II respiratory failure in borderline patients with obstructive airways disease[11]. Gastrostomy feeding may precipite diabetes or increase insulin requirements in established diabetics and therefore blood sugars should be carefully monitored. Nasal intermittent positive pressure ventilation is indicated if enteral feeding results in respiratory failure.

Burkholderia cepacia

It has been suggested that there is a greater post operative mortality for CF patients infected with *B. cepacia*[15]. There

are a number of reports analysing the influence of *B. cepacia* on survival following transplantation with contradictory findings. In an early series of transplantated CF patients, of whom three had been colonized with *B. cepacia* prior to transplantation no additional mortality was observed[1]. The issue of whether *B. cepacia* was a contraindication for transplantation was particularly raised by Snell *et al.* who described a group of 23 cystic fibrosis patients[15]. Of the 15 patients who had *B. cepacia* identified the mortality was 75%. Data from the same transplant programme suggests that CF patients infected with *B. cepacia* also appear to be at risk of greater postoperative morbidity including *B. cepacia* related septicaemia, percarditis, pneumonia and empyemas[16]. However, there is a confounding factor which may explain the excess in mortality reported by Snell *et al.* In Snell's report, 50% of the patients identified with *B. cepacia* had the organism identified for the first time following transplantation. This suggested that there may have been inadequate pre-transplant microbiological surveillance or that the organism was acquired *de novo* following transplantation. The possibility that the patients were colonized with *B. cepacia* and that this was not apparent to the transplant team could have led to inadequate antibiotic strategies following transplantation. Alternatively, the *de novo* acquistion of *B. cepacia* following transplantation in a patient who was immunocompromised may have particular implications from the point of view of the host pathogen interaction. Spread of *B. cepacia* in non CF immunocompromised patients is well recognized[17]. Indeed, it is recognized that transplant centres can be a source for cross infection with *B. cepacia*[18]. Following this report two subsequent reports, one from North America[18] and one from the UK suggested that there was no excess mortality associated with *B. cepacia*[20]. In the report from the UK the combined data from three transplant programmes suggested that 14 patients identified with *B. cepacia* had no excess in mortality[20]. Any mortality observed did not appear to be related to the antibiotic resistant profile. However, *B. cepacia* was not a major pathogenic problem during the years the patients were transplanted. In a report from North Carolina, 12 patients colonized wtih *B. cepacia* were transplanted and there was no excess mortality observed[19]. It is notable that in both of these reports the *de novo* acquistion of the organism following the transplant was not observed. The current situation may in fact be different on the basis of a more virulent strain of *B. cepacia*. More recently there is data from another UK CF centre which suggests that the mortality of their *B. cepacia* patients transplanted, in a variety of centres was in excess of those patients not colonized with *B. cepacia*[21]. The contrast between this and the earlier UK study may reflect the fact that the current population of cystic fibrosis patients have a greater prevalence of *B. cepacia* than patients previously referred for transplantation.

Therefore some *B. cepacia* patients appear to do well while others do badly. Very little is understood about identifying 'at risk patients'. The clinical outcome following transplantation may primarily depend upon the virulence of the organism and the host response to *B. cepacia*. Host factors are often underemphasized. A UK multicentre study has shown that there is an exaggerated host response in the presence of infection with *B. cepacia*; levels of inflammatory markers; C-reactive protein and neutrophil elastase alpha 1-antiproteinase complex were significantly higher during *B. cepacia* infections than during infections due to *P. aeruginosa* alone[22]. The lipopolysacharide of *B. cepacia* can induce inflammatory cytokines including tumour necrosis factor to a level greater than that induced by *P. aeruginosa*[23]. Therefore distinguishing between clinical syndromes associated with *B. cepacia* (progressive disease versus low grade septicaemia) may be most important in predicting the outcome in patients colonized with *B. cepacia* following transplantation.

Nasal intermittent positive pressure ventilation (NIPPV)

The indications for using NIPPV for CV patients awaiting transplantation differ from those for patients with chronic airflow limitation. Previously CF patients developing acute type 2 respiratory failure died rapidly within weeks. Application of the technique of NIPPV to the CF patient in terminal respiratory failure can increase survival for a crucial 6–9 months providing a bridge until donor organs become available[12,13]. The institution of NIPPV for CF patients awaiting transplantation should be early and based upon the inability to deliver sufficient oxygenation rather than when established hypercapnia occurs, this being a late prognostic sign. A judicious anticipatory institution of NIPPV avoids crisis commencement in the very breathless patient who is too distressed to comply with and learn the technique. Following the commencement of NIPPV it is possible to provide adequate supplementary oxygenation without hazard.

Antibiotic therapy

Preservation of pulmonary function with aggressive antibiotic therapy to control pulmonary sepsis is essential prior to transplantation. However, selecting the most effective intravenous antibiotic treatment during these months can be difficult. Inevitably *P. aeruginosa* may show multiple antibiotic resistance and *B. cepacia* may be completely resistant *in vitro* to all antibiotics. Invariably it is necessary to choose an antibiotic regimen which clearly demonstrates *in vitro* resistance but with careful clinical

assessment it can be shown to have an *in vivo* response. Such clinical data is invaluable to the transplant programme when post operative antibiotic regimens are being planned. Eventually some patients will require continuous intravenous antibiotics. For patients requiring continuous intravenous antibiotics, venous access can be improved with totally implantable systems. These can be placed under local anaesthetic and ensure continuation of antibiotic treatment and reduce total hospital dependancy[14]. However, implantable venous access systems are not without their own problems. Complications such as, line associated venous thrombosis can occur and most importantly in the context of future immunosuppression, colonization and infection with *Candida* species can occur. A high index of suspicion is required for the diagnosis of *Candida* associated infection and if it occurs the device needs to be removed and appropriate non-nephrotoxic treatment administered.

Aspergillus fumigatus

Following lung transplantation for all patients a range of *Aspergillus*-related disease has been described and classified[24]. This has included, aspergillus bronchitis, ulcerative tracheobronchitis, pseudomembranous bronchitis and bronchocentric granulomatosis[24,25]. Therefore *Aspergillus fumigatus* (*A. fumigatus*) infection may be associated with high morbidity and mortality following lung transplantation.

Concern has been expressed that preceding colonization with *A. fumigatus* will predispose to postoperative dissemination. This is particularly an issue with CF patients as the usual prevalence of positive sputum cultures for *A. fumigatus* is 20% of adult CF patients. Therefore it is often advised that CF patients colonized with *A. fumigatus* should be treated prophylactically with antifungal agents prior to surgery. However, a recent study has suggested that although there is a high mortality associated with *A. fumigatus* infection in both CF and non-CF patients after transplantation, precolonization was not a risk factor for postoperative infection[19].

Heart/lung or double sequential lung transplantation

Heart–lung transplantation (HLT) was the first reported successful type of surgery but currently, bilateral sequential lung transplantation is increasingly and successfully being performed in many transplant centres[2]. The essential difference between the two types of surgery is that the patient's heart is retained and there are two bronchial anastomoses in the double sequential lung transplant, whereas in contrast, HLT uses the donor's heart and only a tracheal anastomosis is performed. Although HLT gives the opportunity of a Domino operation (another recipient acquires the explanted CF heart) the CF patient receives an unconditioned heart from the donor[26]. This transplanted heart can potentially suffer from graft rejection and its right ventricle may not be sufficiently conditioned to perform optimally in the presence of lung graft failure. By retaining the CF heart in a double sequential lung transplant procedure, the patient retains a right ventricle which has the capacity to function in suboptimal clinical conditions.

The CF patient receives a denervated heart with HLT. Although this is functionally adequate in the long term, early post operatively it is prone to nodal rhythm/sinus arrest, and artrial arrythmias. When an atrial rhythm is established, the transplanted heart inherently runs at a rate of 80–110 beats/min because of the absence of vagal inhibition. The retention of the heart in a double sequential lung transplant may avoid the need for cardiopulmonary bypass. However, bypass may be required during difficult lung dissection at the time of native lung explantation or when the patient is difficult to ventilate on one lung. Bypass also gives rise to heparin-induced bleeding.

Because of the additional anastomosis, the duration of a bilateral sequential lung transplant is substantially longer (mean 327 min) than that of a heart/lung transplant operation (mean 236 min)[27]. This is because extra anastomoses are performed with a double sequential lung transplant. As a result, in a double sequential lung procedure the second lung can receive a significant ischaemic injury. Currently, there is no evidence that this extra ischaemic injury results in a long term failure of graft function[27].

Heart–lung transplantation is performed through a median sternotomy. Dissection and anastomosis are undertaken close to the vagi, recurrent laryngeal and phrenic nerves. Consequently these nerves are potentially at risk of injury during surgery. In bilateral sequential lung transplantation, the anastomoses are undertaken away from the mediastinum so there is less risk of nerve injury.

Nerve injury following heart/lung transplantation is important because patients with CF have reduced gastric emptying, hyperacidity and lax gastroesophageal sphincters. Vagal injury can exacerbate this problem. Vagal injury combined with recurrent laryngeal nerve injury predisposes to a risk of aspiration[28].

Pain relief

The bilateral sequential lung transplant is undertaken through an extensive wound, a bilateral thoraco-sternotomy. This wound gives the surgeons excellent access to the pleural spaces but post operatively it is extremely painful. Adequate analgesia is therefore essential. Non steroidal anti-inflammatory drugs are contraindicated because of the risks of renal impairment. This is critical because aminoglycoside

antibiotics, cyclosporin therapy and diuretics are also nephrotoxic. Narcotic analgesics are often used for pain relief but these should be administered with caution as CF patients are particularly sensitive to their effects. CF patients will often have been in ventilatory failure prior to transplantation requiring NIPPV support, therefore they will have a poor respiratory drive. Therefore narcotics can further impair their drive. Although marginal hypoventilation and CO_2 retention are well tolerated the accompanying atelectasis will increase the risk of infection. The optimal method of analgesia immediately postoperatively, is by the placement (after correction of any coagulopathy) of an epidural cannula.

Weaning

Weaning is dependent on graft function which itself is influenced by, the ischaemic time, reperfusion injury, pre-op donor infection, pre-op recipient pulmonary hypertension, fluid status and ventilatory drive. The application of positive end-expiratory pressure and keeping the patient 'dry' with fluid replacement by colloids rather than crystalloids can reduce the degree of alveolar leakage. In most patients early extubation is advisable but we advocate early tracheostomy for weaning in high risk patients (low weight, NIPPV dependent). This has the advantage of allowing aggressive enteral feeding with reduced risk of aspiration, regular bronchial toilet by bronchoscopy without heavy sedation, and nocturnal ventilatory pressure support.

Ventilatory effort is influenced by post operative pain, narcotics, and pre-transplant ventilatory failure. The removal of the hypoxic drive by the rapid normalization of O_2 levels can reduce ventilatory effort, therefore every effort should be made to reduce the concentrations of oxygen administered during the weaning process.

Nutritional support following surgery

Postoperative feeding is easier with a gastrostomy but if the patient is progressing well, it is advisable to withhold supplemental feeding. In the presence of narcotic analgesia, intercostal drains and other drugs which can induce nausea, early supplemental feeding can often precipitate vomiting, gastric distension and associated diaphragm splinting. To prevent these problems it is advisable to recommence supplemental feeding five to eight days postoperatively. If the patient suffers graft dysfunction and is slow to wean, a feeding gastrostomy is an advantage. Cisapride can be used if there is a problem related to gastric emptying. The combined administration of the imidazole group of antifungal agents and cisapride is contraindicated because of the risk of cardiac arrythmias induced by elevated cisapride levels. In the event of a patient suffering multiple organ failure every effort should be made to feed the patient enterally. Enteral feeding is safer and probably superior to parenteral feeding[29].

If sufficient pancreatic enzyme replacement is used postoperatively intestinal obstruction is not likely to occur. However, if the patient is intubated and a feeding gastrostomy is being used, it is not possible to administer the enzyme pellets through the gastrostomy. In this situation uncoated enzyme powder dissolved in water and injected through the gastrostomy can be used. One gram of powder (e.g. 1.5 ml of Pancrex V, Viokase) is approximately equivalent to three standard strength enteric coated microsphere/mini tablets. Alternatively, uncapsulated but larger enzyme pellets can be injected down a large bore nasogastric tube. If a meconium ileus occurs it can be effectively treated by oral gastrografin 30 ml qds.

Immunosuppression

Immunosuppression regimens vary between transplant programmes. Induction of immunosuppression involves high dose intravenous corticosteroids, azathioprine 4 mg/kg, cyclosporin at a time when renal function is considered to be capable of coping with its introduction and antilymphocyte preparations such as OKT3 and rabbit anthymocyte globulin, (RATG)[30]. OKT3 is one of the most potent immunosupressant agents available, it is a monoclonal antibody directed against T cells[30]. It has the effect of modulating the T-cell receptor complex so that the T cell becomes blinded to the graft antigens[30]. Antithymocyte globulins or antilymphocyte globulin are polyclonal antibodies derived by raising antibodies in animals against human lymphoid cells (i.e. RATG)[30]. ATG is not as specific as OKT3 and reacts strongly with both B and T cells and other cell lines including neutrophils and macrophages. Therefore infection is an important consequence of antilymphocyte preparations[30]. In general, intensive induction of immunosuppression (particularly with antilymphocyte preparations) can reduce the incidence of rejection but invariably at the cost of a higher incidence of infection. This is particularly important in the context of CF patients who have persistent multiresistant organisms in their upper airway. There is no controlled study which demonstrates the benefit of the use of antilymphocyte preparations in the context of improved survival in CF patients undergoing lung transplantation.

A combination of cyclosporin, azathioprine, and corticosteroids is the standard maintenance treatment. Cyclosporin has revolutionized solid organ transplantation. It is an immunophilin binding drug that inhibits the enzyme calcineurin[31]. Calcineurin is a critical link in the steps involved in the engagement of foreign antigen by T-cell receptors which subsequently lead to T cell activation and cytokine transcription[31]. Cyclosporin has variable bowel

absorption which is exaggerated by malabsorption in CF patients[32]. To reduce the risk of fluctuating levels of cyclosporin in the early postoperative period it is advisable to maintain the CF patient on intravenous cyclosporin 1–2 mg/kg per 24 h until such time as the bowel action is normal. On the institution of oral therapy, a three times a day dosage regimen is often required to maintain satisfactory serum levels (200 μg/ml to 300 μg/ml). Serum levels can be potentiated deliberately to reduce the cost of cyclosporin by using concomitant ketoconazole, cimetidine or itraconazole. Neoral, the new commercially available microemulsion formulation of cyclosporin with improved bowel absorption, may be potentially superior for CF patients[33]. Controversy exists as to this interpretation with some solid organ groups reporting a higher incidence of rejection following conversion from 'Sandimmun' to the new preparation Neoral[34]. The Sandimmun preparation will be withdrawn from the market place from early 1997. The strategy for conversion from Sandimmun to Neoral is by a direct dose for dose conversion. It can then be anticipated that there will be an increase in the measured trough cyclosporin level and possibly a rise in serum creatinine. Therefore early testing of cyclosporin levels and the creatinine level is advised within the week, followed by appropriate manipulation of the dose according to the levels. Cyclosporin induced nausea is a common side effect but an additional important side effect is, cyclosporin induced grand mal seizures which generally occur in younger patients (i.e. CF age group). Nephrotoxicity is the most important side effect related to cyclosporin.

Like cyclosporin, tacrolimus (FK506) is an immunophilin binding drug which impairs T cell activity[31]. However, tacrolimus binds to a different receptor called FKBP-12 forming a complex which inhibits calcineurin. It is becoming increasingly popular and has been advocated as being superior to cyclosporin in the context of preventing the development of obliterative bronchiolitis (OB). However there is no clear evidence to support this. Although cyclosporin and tacrolimus have different molecular structure their immunosuppressant properties are very similar. The difference between them is in their molar potency[31]. Tacrolimus has a higher molar potency but also a higher molar toxicity[31]. A direct clinical comparison between tacrolimus and cyclosporin in lung transplant recipients is required with the endpoints including, safety, incidence of lymphoproliferative disease and the impact on OB.

Bronchoscopy

Many CF patients fear post-operative bronchoscopy and transbronchial biopsies (TBB). In view of the persistence of multiresistent organisms in the sinuses of patients with CF, it is standard practice to perform flexible bronchoscopy via the oral route rather than through the nose. Bronchoscopy can document early anastomotic dehiscence and anastomotic stenosis. CF patients appear to be particularly resistant to the short acting benzodiazepine midazolam and often require boluses in the region of 15 mg. To maximize the patients' comfort and reduce the dose of midazolam, the addition of afentynal 250 μg is effective. The main risks from TBB include pneumothorax and biopsy related bleeding[35], but the risk of these are low because thoracotomies induce a degree of pleurodesis and a transplanted lung has a reduced vascular supply. Denervated transplanted lungs make flexible bronchoscopy and TBB easier because the cough reflex is absent[36].

Rejection surveillance

Regular surveillance bronchoscopy and TBB has prevailed in many programmes, initially based on data published from the Papworth group[37]. This policy has now been re-evaluated and there is an increasing trend towards TBB being performed only in the first six months following transplant and thereafter only in the event of a decline in lung physiology or when the patient has symptoms. Whether regular surveillance TBB is superior to biopsy on the basis of clinical indications, in reducing the incidence of post transplant obliterative bronchiolitis is unresolved. It is our policy to perform an early TBB and on the basis of this result, to characterize a patient as being a 'rejector' or a 'non-rejector'. Rejectors are then treated with augmented immunosuppressions (increased steroids, augmented cyclosporin levels, and or methotrexate as an additional therapy) and regular TBB (every two weeks) until there is no evidence of rejection on histology. Rejectors are then biopsied on the basis of symptoms and changes in lung physiology in exactly the same way as non-rejectors. There is no published data to suggest that this strategy is superior to any other approach.

Infection prophylaxis

After transplantation, there is a risk of infection due to pulmonary denervation and impaired ciliary function[36]. CF patients should therefore perform chest physiotherapy twice daily. Although CF patients have a high prevalence of multiresistant *Pseudomonas*, *Aspergillus* and *Candida* colonization prior to transplantation, risk of post transplant opportunistic infection is comparable in non-CF recipients and CF allograft recipients[19]. Infection is an important treatment issue because the commonest cause of early death in the first year is infection with multiple organ failure[2].

Pre-transplant antibiotic resistance patterns allow the administration of appropriate gram negative dual therapy. Aminoglycosides are the cornerstone of the regime and do not adversely affect renal function provided drug levels are

carefully monitored. Diuretics, however, have the potential to augment aminoglycoside toxicity. Ototoxicity is a risk if aminoglycosides are used in combination with other ototoxic agents, such as ganciclovir. Infection control policies are important for patients colonized with *B. cepacia*, because the *de novo* acquisition of this organism by other CF patients following transplantation may carry a particularly high mortality[15]. Prophylactic nebulized antibiotics (colomycin, tobramycin) can be used to reduce the bacterial load in the remaining native upper airway of the CF transplant recipient. This is delivered using a Ventstream PZ nebulizer with a sealing face mask (e.g. Medic Aid, Pagham, Sussex). This system has the advantage of increasing the proportion of central deposition and together with a filter protects the ward environment from exhaled antibiotic.

Methillicin-resistant *Staphylococcus aureus* (MRSA) is not an uncommon colonizing organism but there is no evidence that its presence is a contraindication to surgery. If a patient is a carrier it is mandatory for the transplant team to be aware of this in order to instigate strict infection control policies during the operation and in intensive care.

Aspergillus fumigatus

Early postoperative infection with *A fumigatus* is unusual. In view of the morbidity associated with *A. fumigatus* many programmes use prophylactic regimens directed against *A. fumigatus*. Low dose oral itraconazole prophylaxis is not useful as its effects are dependent on appropriate serum levels being achieved, therefore a standard dose (200 mg tds) is required. Itraconazole interacts with cyclosporin and if it is used the total daily dose of cyclosporin should be reduced to a quarter the standard dose. Nebulized amphotericin B is a useful prophylactic agent, but is troublesome to use in a sealed intensive care unit because staff are exposed to the exhaled drug. If nebulized amphotericin B is indicated it is our practice to ensure exhaled drug is ventilated via a filter (*see above*). Although expensive, intravenous liposomal amphotericin is an advance for the treatment of fungal infection. Liposomal delivery of amphotericin, allows the administration of 5 mg/kg of amphotericin without the nephrotoxicity of amphotericin B. Systemic intolerance (pyrexia, rigors, back pain) can still occur but this can be minimized by the concurrent administration of an antihistamine and paracetamol.

Cytomegalovirus

The prevalence of cytomegalovirus (CMV) seropositivity increases with age and by the third decade about 20% of the general population can be expected to be CMV seropositive. Therefore many CF patients are CMV seronegative. CMV infection or disease (i.e. pneumonitis) carries a high morbidity and mortality, particularly if seronegative CF recipients receive an organ from a donor who is CMV seropositive. All transplant programmes use CMV serostatus in their donor/recipient matching criteria. However, if a CF patient is desperately ill this matching policy can be overridden. Antiviral prophylaxis is then indicated to reduce the risk of CMV disease. CMV prophylactic regimens vary between transplant centres. A prolonged course is probably required (up to 120 days post transplant) as is the case in allogenic bone marrow transplant recipients. Alternative strategies include combined antiviral therapy and hyperimmunoglobulin, intermittent doses of ganciclovir (alternate days), and perhaps in the future oral ganciclovir and valacyclovir. Rapid early diagnosis using techniques like CMV antigenaemia have greatly improved the diagnosis and management of CMV infection[38,39].

Post transplant lymphoproliferative disease

Post transplant lymphoproliferative disease (PTLD) occurs in up to 8% of heart/lung transplant recipients[40]. PTLD is the result of clonal proliferation of B cell lymphocytes in the presence of T cell suppression by cyclosporin. Epstein–Barr virus (EBV) infection is also believed to be an important trigger for the proliferation of B cells. Primary EBV infection in the recipient (i.e. the donor was EBV positive and the recipient EBV negative) is also a risk factor for the development of PTLD. Immunosuppression is the key factor in the development of PTLD and EBV a cofactor[41]. This is suggested by epidemiological evidence which demonstrates that PTLD is more common in solid organ transplant recipients in the USA in comparison to Europe. This mirrors a trend for heavier immunosuppressive protocols within the USA[42]. Furthermore, ganciclovir prophylaxis regimens aimed at CMV but which are also effective against EBV do not appear to have impacted on the incidence of PTLD. The sites for the development of PTLD are protean but in lung transplant recipients it commonly presents within the graft[40]. This suggests that bronchus associated lymphoid tissue may be an important site for the initiation of the proliferation of B cells. This is further suggested by a report documenting PTLD presenting as an ulcerative bronchitis[43]. The commonest radiological changes is that of circumscribed masses within the lung tissue (Figure 1). The differential diagnosis of such lesions in a transplant recipient includes *A. fumigatus*, therefore an open biopsy may be required to secure the diagnosis. The first line of treatment for PTLD is a drastic reduction in the level of immunosuppression and the treatment of local disease (radiotherapy, surgery). If there is no response the outlook is poor. This is often the case with monoclonal high grade B cell lymphomas. Chemotherapy offers poor results and carries a high morbidity in the context of *A. fumigatus*.

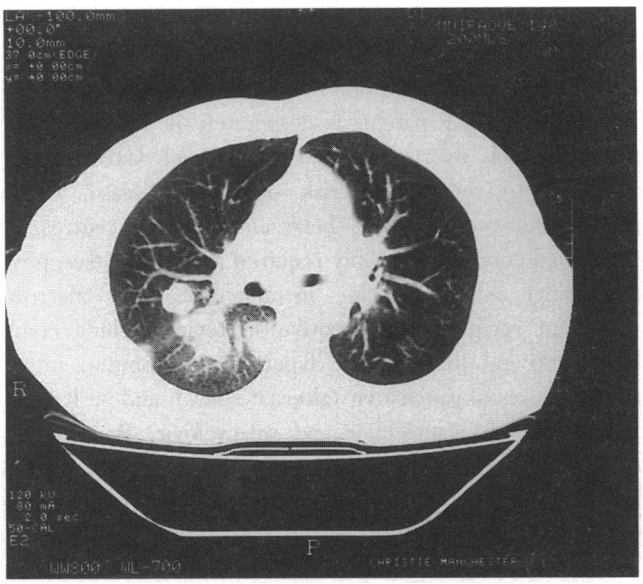

Figure 1 **A thoracic CT scan of a heart/lung transplant recipient eight months following transplantation. This demonstrates three nodules, 2 cm in diameter in the right lower lobe. An open lung biopsy confirmed the diagnosis of high grade B cell lymphoma**

Table 2 **The functional classification of Bronchilitis Obliterans Syndrome**

Stage		FEV_1 of Baseline	Without histological evidence	With histological evidence
BOS 0		>80%	a	b
BOS 1	Mild	66% to 80%	a	b
BOS 2	Moderate	51% to 65%	a	b
BOS 3	Severe	50% or less	a	b

For example: Consider a patient following a double lung transplant whose peak FEV_1 at a time following transplantation is 3.0 L (the normal predicted FEV_1 for sex and height is 2.0 l). The patient develops graft dysfunction with physiological small airways obstruction and a FEV_1 of 1.5 l. Repeated transbronchial biopsies show no histological evidence of obliterative bronchiolitis and there is no evidence of active infection. This patient has BOS grade 3a. The FEV_1 of 3 l is the reference point, not the predicted of 2.5 l

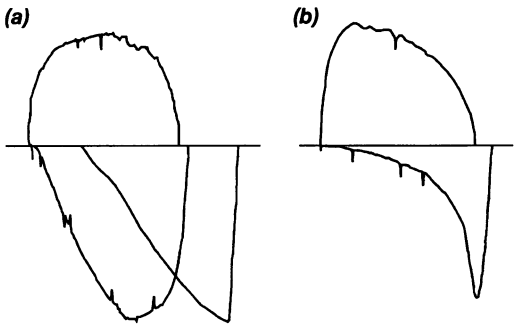

Figure 2 **This is the flow volume loop of a patient following a double sequential lung transplant who developed bronchiolitis obliterans. The normal flow volume loop A was recorded six months following transplantation. Flow volume loop B was recorded 15 months following transplantation. This shows the normal inspiratory phase above the horizontal line followed by forced expiratory flow below the line. There is evidence of small airway obstruction**

Obliterative bronchiolitis

The gradual decline in survival after the first year following lung transplantation results largely from the development of OB[2]. The diagnosis of OB can be difficult and does not require histological confirmation. Therefore the International Society for Heart and Lung Transplantation have designated that graft failure as a result of OB should be considered a syndrome and referred to as Bronchiolitis Obliterans Syndrome (BOS)[44]. In order to standardize the clinical assessment of OB a staging system has been devised (Table 2)[44]. This acknowledges that transbronchial biopsy is not required for the diagnosis of OB, in fact changes in FEF 25–75 is the most sensitive way for diagnosing OB[45]. It is important to acknowledge that BOS is a heterogenous clinical condition and as a result, therapeutic trials in small patient groups are difficult to interpret. Increasingly BOS is acknowledged as a pan airway problem which manifests clinically as irreversible small airway obstruction (Figure 2a, 2b). The evidence for this is provided by studies of large airway bronchial biopsies which show increased T cell expression within the bronchial mucosa in comparison to normal controls[46]. Furthermore high-resolution computerized tomography (HRCT) of patients with BOS demonstrated bronchial dilatation or bronchiectasis in the graft suggesting that low grade chronic infection may also play a role in the development of the syndrome. An infective component of the process may explain why augmented immunosuppression has only limited success in the management of BOS. Early and recurrent acute cellular rejection and lymphocytic bronchiolitis are risk factors for the development of OB emphasizing that the development of BOS is an expression of lung injury probably emanating from more than one aetiology. Ultimately each individual or combination of aetiological factors (infection, ischaemia, immune injury) may result in a common clinical and histological response to injury.

Cryptogenic Organizing Pneumonia (COP)

Bronchilitis obliterans and organizing pneumonia (BOOP) is another important cause of graft failure following lung transplantation. However, the term BOOP in the context of transplantation is confusing. Cryptogenic Organizing Pneumonia (COP) is a more accurate term and is synonymous with BOOP. COP is characterized by a restrictive flow volume loop and bilateral radiological alveolar shadowing in the absence of demonstrable infection or aspiration. The restrictive physiology of COP contrasts

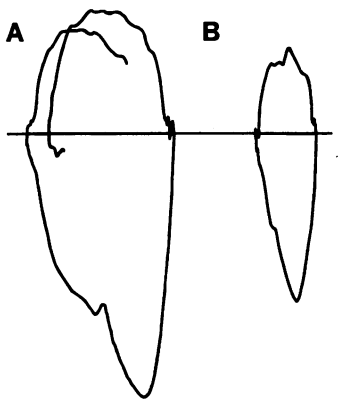

Figure 3 **This is the flow volume loop of a patient following a heart/lung lung transplant who developed cryptogenic organizing pneumonia. The normal flow volume loop A was recorded eight months following transplantation. This shows the normal inspiratory phase above the horizontal line followed by forced expiratory flow below the line. Flow volume loop B was recorded 12 months following transplantation. This demonstrates a flow volume loop with the same shape as loop A but with a restricted flow, typical of cryptogenic organizing pneumonia**

with the flow volume loop of small airways disease (Figures 2, 3). The indentification of COP has an important prognostic implication. At the Wythenshawe Hospital transplant programme, in those patients identified as having isolated OB the survival following transplantation is different to those initially identified as having COP who later progress to OB (Figure 4)[47]. Whether COP is a manifestation of rejection or is a surrogate marker for an individual who mounts an aggressive fibroproliferative response to a variety of injuries is unclear. The treatment of COP in the absence of infection involves augmented immunosuppression particularly in the form of corticosteroids which are particularly prone to inducing subsequent fungal infection.

Treatment of Bronchiolitis Obliterans Syndrome (BOS)

There is no widely accepted optimal treatment for BOS. There are advocates for a number of different types of treatment but because BOS is a heterogenous condition with a variable natural history, observed in a heterogenous group of recipients (CF, emphysema, pulmonary fibrosis, pulmonary hypertension) interpretation of published data is difficult. However, augmented immunosuppression in the context of 'rescue treatment' is generally the rule. This can take the form of an acute rescue regimen of antilymphocyte preparations including RATG or OKT3. Rescue therapy in the form of a switch from cyclosporin to tacrolimus has also been advocated. The addition of methotrexate is also practised in some centres. Total lymphoid irradiation (TLI) is increasingly practised for refractory acute rejection and BOS[48]. Invariably the results suggest that rather than reversing the process of BOS, treatment strategies predominantly impact on the rate of decline of graft function. At the Wythenshawe Hospital transplant pro-

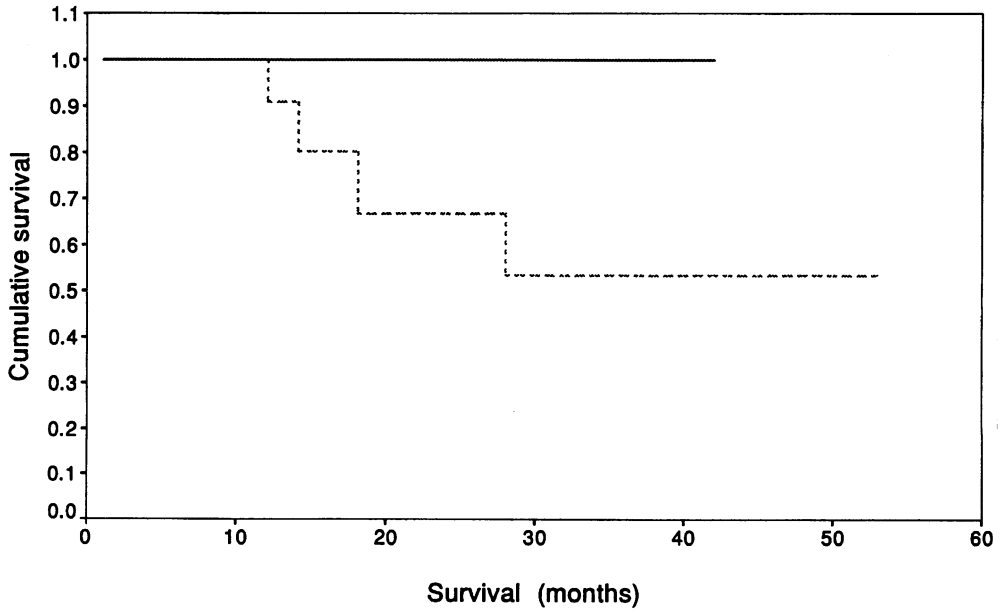

Figure 4 **Survival function: this is the Kaplan–Meier survival curves of patients attending the Wythenshawe Hospital transplant programme with isolated bronchiolitis obliterans (OB) (continuous line) and those with cryptogenic organizing pneumonia (COP) who progressed to Bronchilitis Obliterans Syndrome (broken line). The survival of those patients with COP is reduced compared to patients with isolated OB although this difference is not significant**

gramme a step wise approach to treatment is offered to patients with a diagnosis of BOS. Phase 1 treatment for BOS stage 1 and 2 includes RATG 1.5 mg/kg for three consecutive days with 150 mg of methylprednisolone per day. Phase 2 treatment for BOS stage 1 and 2 occurs 14 days following RATG, when low dose methotrexate 2.5 mg three times per week is introduced in conjunction with high dose inhaled steroids 500 μg twice daily. Phase 3 treatment for BOS stage 2 and 3 includes TLI. This involves a planning visit followed by treatment to nodal areas on three consecutive days with a dose of 2 Gy each day.

Invariably this type of protocol has an impact on the patient's quality of life in the context of an inevitably fatal illness. Therefore on the basis that BOS is a terminal illness phase 4 treatment, involves a strategy of palliative care for BOS stage 3. This includes: rehabilitation in the form of a lower limb exercise programme, chronic oxygen therapy, regular nebulized anticholinergic therapy, regular home intravenous antibiotic therapy for the inevitable superimposed bacterial infection, nutritional support and morphine therapy for distressing breathlessness.

Retransplantation is considered for each individual case. However, on the basis of the poor results of retransplantation this strategy is only offered to a minority[2]. The criteria required for retransplantation include: (a) the absence of active infection (unusual with BOS 3); and (b) a creatinine clearance of >50 mL/min (unusual following chronic cyclosporin therapy).

Donor issues

The poor results of retransplantation focuses us on the lack of donors of all patients particularly patients offered transplantation for the first time. With an ever increasing number of adults with CF dying from terminal lung failure, the demand for lung transplantation is rising exponentially. However, it is estimated that over the next decade that the demand for lung transplantation from cystic fibrosis patients will only partially be satisfied[49].

Despite improved trends in solid organ donation in the United Kingdom in the 1980s there has been a small but significant decline in solid organ donations in the early 90s. In the general population the rates of death from road traffic accident and intracranial haemorrhage have decreased because of active strategies to resolve these problems. Furthermore the greater availability of sophisticated radiological techniques have allowed a more accurate estimation of patient survival following intracranial events. This may have had the effect of reducing the number of potential donors being ventilated for consideration of active neurosurgical treatment. This trend is possibly, further potentiated by the limited resource of available intensive care beds.

It is notable that there is great variability between regions of the country for rates of lung donation. In 1994 there were 7.1 per million population (PMP) cadaveric thoracic organ donations made in the North West of England, in comparison to 9.8 PMP for the Northern/Yorkshire region. In contrast there were 26.4 PMP cadaveric renal transplant donations in the North West of England, in comparison to 31.9 PMP for the Northern/Yorkshire region[50]. The fact that donor rates vary suggests that local factors may result in an unequal emphasis on the promotion and management of multiorgan donations in different regions throughout the country[50,51].

As a consequence new approaches have been advocated. Strategies of education aimed at medical and nursing staff in order to improve donors' rates have been studied. The impact of staff education in the skills of dealing with donors has been evaluated under the auspices of the European Donor Hospital Education Program (EDHEP)[52]. The results of EDHEP are encouraging from the point of view of kidney transplantation but further evaluation is required to confirm that the benefit is seen with respect to lung transplantation[52]. In Spain there has been a 40% increase in the rate of organ donation on the basis of constructing a widespread coordination network which focuses on donor detection rather than retrieval[53]. The thrust of this strategy is the early detection of potential donors which facilitates skilled family communication and donor management protocols at an early stage[53].

However, increased rates of donation does not necessarily equate with optimal donor utilization. Donor utilization is influenced by other factors including the availability of specialist staff, the availability of intensive care beds, space in the donor hospital and intensive care bed occupancy in the transplant hospital. Such issues may go some way to explain the difference in donor utilization seen across the country.

In response to these problems Dr Starnes' group in Los Angeles have pioneered living related lung transplantation[54]. This involves two potential living donors, each individual donating one lower lobe. After donation, each lobe is then transplanted into the ipsilateral hemithorax of the CF patient whose CF lungs have been removed. The selection of potential recipients and donors for living related transplantation requires close attention. Absolute precluding factors include, two CF siblings in the family, if a donor is a smoker, if there is ABO incompatability, if the recipient is colonized with *B. cepacia*.

Clearly it has to be demonstrated that there has been no coercion of the potential donor by the family or medical staff. To protect against this we advise two independent assessments of the potential donors and recipients. This assessment should be carried out by an independent physician and an independent psychiatrist not involved with

the transplant programme. This is aimed at ensuring that the donors and recipients are aware of the medical, social and financial implications to the family in the event of an unforseen complication. For instance the insurance implications for a working father, who through the screening procedure was noted to have a significant occult illness. Should the process be deemed appropriate a mandatory 'cooling off' period of two weeks is required to facilitate any change of mind.

The early results reported by the Los Angeles group suggest that living related lung transplantation offers an alternative in a small and highly selected group of cystic fibrosis patients awaiting transplantation[54]. However, it is not likely to be the panacea for donor related problems.

Conclusion

Lung transplantation currently offers the only means of survival for CF patients with preterminal pulmonary disease. Effective communication between the pre and post transplant medical teams, ensures continuity of complex medical care, thereby offering these patients the opportunity of optimal survival and a good quality of life following transplantation.

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