The medical management of patients with cystic fibrosis following heart-lung transplantation


The medical management of patients with cystic fibrosis following heart-lung transplantation. B.P. Madden, K. Kamalvand, C.M. Chan, A. Khaghani, M.E. Hodson, M. Yacoub. @ERS Journals Ltd 1993.

ABSTRACT: Transplantation for end-stage respiratory failure in cystic fibrosis (CF), with encouraging medium-term results, is now possible. This paper details the postoperative medical treatment required by these patients.

The management of 79 patients who underwent heart-lung transplantation is described. Details of intensive care, postoperative care, long-term follow-up, and the problems specific for cystic fibrosis patients are reported.

The duration of care in the Intensive Care Unit (ICU) was 1–93 days (median 5 days). Intubation was required for 7 h to 93 days (median 48 h), and 11 patients required haemofiltration. High doses of cyclosporin A (mean 22 mg·kg⁻¹·q.d.) were required. Acute rejection was common. There were 133 episodes of infection: bacterial 115, viral 11, and other organisms 7. Grand mal seizures occurred in 10 patients, lymphoproliferative disorders in 4, and obliterator bronchiolitis in 17. The median duration of hospital stay was 32 days.

Despite having a multi-system disease, patients with CF can be successfully transplanted, if detailed attention is paid to their complex medical management.

Eur Respir J., 1993, 6, 965–970.

The first detailed description of cystic fibrosis (CF) was made by Andersen [1], in 1938. It is a multisystem disease, the major manifestations of which are chronic bronchopulmonary infection, malabsorption, and a high sweat sodium. There is a high incidence of diabetes mellitus, and the majority of adults are colonized by Pseudomonas aeruginosa, in both upper and lower respiratory tracts [2, 3]. The major cause of mortality in this condition is end-stage respiratory failure, and it was against this background that the possibility of lung transplantation became a promising therapeutic option. The first successful heart-lung transplant (HLT) operations for CF were performed in the UK in October 1985 [4, 5]. Since then, encouraging results with bilateral lung transplantation for CF have been reported [6]. The actuarial survival of the first 79 patients with CF who underwent HLT at our unit, at 1, 2 and 3 yrs was 69, 52 and 49%, respectively [7]. The longest surviving patient is now at 6.5 yrs post-HLT.

The purpose of this paper is to review in detail the medical management of these patients and their follow-up. The long-term follow-up is performed by our unit in collaboration with the local physicians.

Patients and methods

Between September 1984 and March 1991, 79 patients with CF underwent HLT in our unit. There were 39 males and 40 females, whose age range was 8–43 (median 23) yrs. Seventy six patients underwent HLT, and three combined heart-lung-liver transplantation. The indications for surgery were severe respiratory failure and severely impaired quality of life, despite the best available medical treatment. Contraindications to HLT in our unit included active aspergillus or mycobacterial infection, non-compliance with treatment, long-term prednisolone therapy in excess of 10 mg·day⁻¹, and other end-organ failure (unless this was also amenable to treatment at the time of transplantation, e.g. by performing a combined heart-lung-liver transplant).

Features which are important to all HLT recipients, namely intensive care management, immunosuppression, indications for bronchoscopy, acute rejection episodes, management of infection, grand mal seizures, Table 1. – Specific challenges following HLT in CF patients

| 1. | Nutrition |
| 2. | Salt loss |
| 3. | Meconium ileus equivalent |
| 4. | Malabsorption of cyclosporin A |
| 5. | Diabetes mellitus |
| 6. | Persistent infection in the upper respiratory tract |
| 7. | Liver disease |
lymphoproliferative disorders, obliterative bronchiolitis, and miscellaneous events, will be considered. The duration of hospital stay is recorded. In addition, the management of problems specifically encountered in CF patients undergoing HLT (table 1) will be reported. The programme for the long-term follow-up for these patients is outlined.

Results

Intensive care management

The range of time spent on the Intensive Care Unit (ICU) was 1–93 days (median 5 days), and 11 patients required haemodialfiltration for treatment of acute renal failure.

Immunosuppression. Patients were routinely immuno-suppressed with cyclosporin A (CSA), initially given intravenously to obtain levels of 500 ng·ml⁻¹ in the first postoperative month (whole blood monoclonal antibody assay). When bowel sounds returned, CSA was given orally, and methylprednisolone, 125 mg i.v. b.i.d., was prescribed until CSA levels of 300 ng·ml⁻¹ were attained. If patients were intolerant of CSA on account of impaired renal function (serum creatinine >200 μmol·l⁻¹), prednisolone (1 mg·kg⁻¹ q.d., reducing by 5 mg·day⁻¹) was given, until CSA could be reintroduced (when serum creatinine fell below 180 μmol·l⁻¹). In addition, patients received azathioprine, 2 mg·kg⁻¹ q.d., and rabbit anti-thymocyte globulin, 100 mg on alternate days, for the first 10 postoperative days.

Ventilation. All patients were ventilated on an ICU ventilator (Siemens Servo C, Engstrom Ericas), aiming to maintain blood arterial oxygen saturations in excess of 90%, and mixed venous oxygen saturations (SvO₂) between 65–70%. While on the ventilator, patients were sedated with propofol infusion, 200 mg·h⁻¹, and low dose papaveretum, or intermittent papaveretum and midazolam. They were weaned from ventilatory support and extubated as soon as possible after surgery. The range of time spent on a ventilator was 7 h to 93 days, with a median of 48 h.

Inotropic support. Treatment was adjusted to maintain the lowest possible mean pulmonary capillary wedge pressure, to achieve satisfactory tissue perfusion and renal function. In practice, dopamine was given at a dose of <5 μg·kg⁻¹·min⁻¹ for renal perfusion and, if necessary, adrenaline for inotropic support. All patients received a dopamine infusion while in ICU, 27 also received adrenaline, nine isoprenaline, nine noradrenaline, five enoximine and three glyceryl trinitrate.

Infection prophylaxis. Patients received appropriate dual anti-pseudomonal antibiotics for the first 10 postoperative days. The choice of drugs depended on the immediate preoperative sputum culture and sensitivity result. Where possible, aminoglycosides were avoided, because of potential synergism with CSA in producing nephrotoxicity. Flucoxacinill was given intravenously, whilst central lines and chest drains were in situ. All positive sputum cultures were treated with antibiotics for the first two postoperative months and, thereafter, only patients with clinical evidence of lower respiratory tract infection were treated. All patients were prescribed life-long colistin sulphate inhalational therapy, 1 megaunit b.i.d., via a face mask to prevent contamination of the transplanted lung from the upper airway. Co-trimoxazole, 960 mg b.i.d. every third day, was given as prophylaxis against Pneumocystis carinii. In addition, the patients received acyclovir, 200 mg orally q.i.d., and nystatin, 100,000 units orally q.i.d., during the first three post-operative months. Reverse barrier nursing was not employed in the ICU.

Nutrition. Feeding was commenced as soon as bowel sounds returned. Seventy one patients were diagnosed as having malabsorption prior to surgery, and nine had gastrostomy feeding tubes inserted prior to surgery. Twenty patients required nasogastric feeding, with elemental diet supplemented with carbohydrate and medium chain triglycerides. Only those patients who developed meconium ileus equivalent (𝑛=12) received N-acetylcysteine, given orally and by enema. Five patients had gastrostomy tubes inserted after surgery, to augment their calorie intake. Total parenteral nutrition was necessary in 12 patients, but conversion to enteral feeding was made as soon as possible to minimize the risk of infection.

Thirty seven patients required insulin by infusion immediately post-surgery. This includes 20 patients, in addition to the 17 who were known to have diabetes mellitus preoperatively.

General postoperative care

Immunosuppression. After the first postoperative month, the dose of CSA was adjusted to attain levels of 250–350 ng·ml⁻¹, renal function permitting. On account of malabsorption, patients with CF required higher doses of CSA than non-CF HLT recipients. The mean dose of CSA (mg·kg⁻¹ q.d.) at 6, 12, 24 and 48 months after surgery was 22.4, 22.1, 16.7 and 17.1, respectively. The dose of CSA required was significantly less after the second postoperative year (p=0.01). Azathioprine was continued at a dose of 2 mg·kg⁻¹ q.d., provided the white cell count remained above 4×10⁹ cells·l⁻¹.

Indications for bronchoscopy. All patients underwent routine bronchoscopy between the 7th and 10th postoperative days, to inspect the tracheal anastomosis. Thereafter, fiberoptic bronchoscopy was only performed if there was a clinical indication, such as cough, reduction in lung function, abnormality on chest radiograph or pyrexia. At bronchoscopy, "trap" sputum and bronchoalveolar lavage specimens were routinely taken and sent for culture and sensitivity, opportunistic pathogen screen and immunocytochemistry. Three transbronchial lung biopsies were taken, using cupped forceps, from the right lower lobe (unless there was localized shadowing elsewhere on chest radiograph), and sent for histology and culture.
Acute rejection. Acute rejection episodes were diagnosed by a combination of clinical and radiological features, in conjunction with inspection of transbronchial lung biopsy specimens. Clinical features of acute rejection include cough, dyspnoea, reduction in lung function and pyrexia. The chest radiograph can be normal, or demonstrate interstitial shadowing, septal lines or pleural effusions. Transbronchial lung biopsies typically demonstrate peri-vascular cuffing with mononuclear cells [8]. Episodes of acute rejection were most common during the first three postoperative months, when 92% of patients experienced at least one such episode. Thereafter, the incidence of acute rejection decreased with time, so that between 7–12, 13–24 and 25–36 months post-HLT, 74, 84 and 82% of patients, respectively, experienced no acute rejection episodes. No patient experienced an episode of acute rejection after 36 months. Treatment of acute rejection consisted of intravenous methylprednisolone, 1 g-day-1 on three consecutive days for adults; 10 mg·kg-1 q.d. for children.

Infection. Bacteria causing respiratory infection in these patients are shown in table 2. The treatment was routine antimicrobial therapy.

Two patients developed infection with Mycoplasma pneumoniae, which presented with cough, fevers, reduction in lung function, fall in oxygen saturation, and bilateral diffuse interstitial shadowing on chest radiograph. Both were successfully treated with doxycycline.

The commonest viral pathogen was cytomegalovirus (CMV), which caused pneumonitis in 11 patients. The diagnosis of CMV infection was made by a combination of clinical features (pyrexia, malaise +/- lymphadenopathy and hepatosplenomegaly); radiological abnormalities (diffuse interstitial shadowing, pleural effusions); serological investigations (presence of immunoglobulin M (IgM) to CMV and >fourfold rise in immunoglobulin G (IgG) to CMV, detection of early antigen fluorescent foci (DEAFF test for CMV), and histological examination of transbronchial lung biopsy specimens (demonstrating CMV inclusion bodies). Treatment was with intravenous ganciclovir 10 mg·kg-1 q.d., given in two divided doses. Infection was due to Aspergillus fumigatus in four patients. One required intravenous amphotericin B due to invasion, and the others were treated with itraconazole orally and nebulised amphotericin. One patient had Candida albicans, and one atypical mycobacterial infection. There were two cases of glandular fever, which were treated successfully with acyclovir (800 mg orally, five times a day for two weeks), and one of herpes simplex encephalitis (in a patient presenting with grand mal seizures), which was also successfully treated with acyclovir.

One patient developed pneumonia due to Pneumocystis carinii, which responded to oral co-trimoxazole, 1.92 g q.i.d. for three weeks, in addition to pentamidine isethionate, 600 mg q.d. by nebulizer. One patient presented with pyrexia and generalized lymphadenopathy with splenomegaly due to Toxoplasma gondii, and was successfully treated with a combination of oral sulphadiazine, 50 mg·kg-1 q.d., and pyrimethamine, 0.5 mg·kg-1 q.d., for six weeks. During this time, folic acid 15 mg·day-1 was given twice a week. One patient had an episode of enteritis, due to Clostridium difficile, requiring oral vancomycin therapy, and one required cryotherapy for painful vulval condylomata. Eleven patients died from infection, two from septicemia, one from a brain abscess and the remainder from pulmonary sepsis.

Grand mal seizures. Ten patients developed grand mal seizures (table 3). Seizures of metabolic origin were successfully treated by correcting the biochemical derangement. The patient with herpes simplex encephalitis required phenytoin for three months to control seizures. The patient in whom seizures occurred in association with the cerebrovascular accident required anticonvulsants, but subsequently died from intracerebral haemorrhage.

Lymphoproliferative disorders. Four patients developed lymphoproliferative disorders, all of which occurred within the first postoperative year. Three were B-cell disorders confined to the thorax, and all three were initially discovered on routine chest radiograph, the patients being otherwise asymptomatic. The diagnosis was confirmed by percutaneous biopsy under computerized tomographic (CT) scan guidance. Histopathological examination was consistent with a lymphoproliferative disorder, and the lymphocytes expressed Epstein-Barr viral nuclear antigen on their surface. All three patients were successfully treated by a combination of reduction in immunosuppression and high dose acyclovir therapy (500 mg i.v. t.i.d. for two weeks, followed by 800 mg five times a day orally for four weeks). One patient had a T-cell disorder, which presented as a generalized rash with oral ulceration, generalized lymphadenopathy and hepatosplenomegaly. The patient was successfully treated by reduction in immunosuppression alone [9]. Of the three patients who developed a B-cell disorder, one is

<table>
<thead>
<tr>
<th>Organisms</th>
<th>Time after transplantation months</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0-6</td>
</tr>
<tr>
<td>Pseudomonas aeruginosa</td>
<td>54</td>
</tr>
<tr>
<td>Staphylococcus aureus</td>
<td>19</td>
</tr>
<tr>
<td>Haemophilus influenzae</td>
<td>7</td>
</tr>
<tr>
<td>Streptococcus pneumonia</td>
<td>5</td>
</tr>
</tbody>
</table>

Table 3. Causes of grand mal seizures (n=10)

<table>
<thead>
<tr>
<th>Cause</th>
<th>Count</th>
</tr>
</thead>
<tbody>
<tr>
<td>High cyclosporin levels (&gt;400 ng·ml-1)</td>
<td>4*</td>
</tr>
<tr>
<td>Hypomagnesaemia</td>
<td>2</td>
</tr>
<tr>
<td>Hypoglycaemia</td>
<td>1</td>
</tr>
<tr>
<td>Herpes simplex encephalitis</td>
<td>1</td>
</tr>
<tr>
<td>Intracerebral bleeding</td>
<td>1</td>
</tr>
<tr>
<td>Unknown cause</td>
<td>1</td>
</tr>
</tbody>
</table>

*: two of these had hypomagnesaemia.
alive 40 months after successful treatment of the disorder, and two died, one five months later after redo HLT for obliterative bronchiolitis, and the other four weeks later from infection.

**Lung function and obliterative bronchiolitis.** In general, lung function improved quickly during the first three months after HLT, giving a substantial improvement over pretransplant levels [10]. At the time of acceptance for surgery, mean forced expiratory volume in one second (FEV<sub>1</sub>) was 22% predicted, and mean forced vital capacity (FVC) was 35% predicted. At 1, 2 and 3 yrs post surgery FEV<sub>1</sub> was 67, 70 and 60%, and FVC was 71, 70 and 66% respectively.

Obliterative bronchiolitis is diagnosed clinically, with presenting features which include cough, reduction in exercise tolerance and a deterioration in lung function. Physical examination may be normal, or may reveal coarse crackles on pulmonary auscultation. The chest radiograph may be normal, or demonstrate hyperinflated lung fields. The condition may be a manifestation of chronic graft rejection, or perhaps be associated with viral infection, such as CMV. Seventeen of our patients developed this complication. The cumulative probability (70% confidence interval) of having this complication at 1, 2 and 3 yrs post surgery was 17% (12–23), 23% (16–29), and 48% (38–59), respectively, (fig. 1). Seven were treated medically with augmented immunosuppression (e.g. prednisolone for two weeks, 1 mg·kg<sup>−1</sup> q.d., then reducing by 2.5 mg·day<sup>−1</sup> to 0.2 mg·kg<sup>−1</sup> q.d. maintenance), and of these five are stable, one is deteriorating, and lung function returned to normal in one patient. Five patients were retransplanted, three are currently awaiting retransplantation, and two died awaiting retransplantation.

**Duration of hospital stay.** Eighteen patients died in the early postoperative period. Of the 61 patients who were discharged from hospital following HLT, the range of hospital admission was 12–165 days, with a median of 32 days.

**Miscellaneous events.** Ten patients underwent subsequent thoracotomy following HLT for bleeding, and three underwent laparotomy (one for a subcapsular haematoma of the liver; one for an ischaemic small bowel resection; one for peritonitis). One patient developed obstruction secondary to stenosis at the level of the superior vena caval anastomosis, and required surgical correction. Four patients developed a vocal cord palsy (one was bilateral), and one developed elevation of the hemidiaphragm secondary to a phrenic nerve injury. Two patients required electrical cardioversion of arrhythmias (atral fibrillation in one, and supraventricular tachycardia in one). One patient developed acute arthropathy and purpura associated with an elevation in serum immune complex level, and one developed severe acute thrombocytopenia related to azathioprine therapy. One patient developed an area of dehiscence at the posterior aspect of the tracheal anastomosis, which settled completely on antibiotic therapy alone.

**Problems specific for cystic fibrosis (table 1).** Seventy one patients were known to have malabsorption preoperatively. At the time of surgery, the percentage predicted mean body weight for the group was 78.1%. Corresponding values at six months (n=44), 12 months (n=31), 24 months (n=18) and 36 months (n=10) were 84.6, 85.1, 84.2 and 89%.

Patients with lower percentage predicted body weight at the time of surgery did not have increased mortality following HLT. The problems associated with hyponatraemia, meconium ileus equivalent, persistent infection in the upper respiratory tract and cyclosporin A requirements in this group of patients have already been described. Diabetes mellitus was well controlled after surgery, as exercise capacity improved considerably, and the frequency of lower respiratory tract infections was significantly reduced. Patients with diabetes mellitus preoperatively did not have increased mortality following HLT.

Fifty one patients had normal preoperative liver function. This remained normal in 23 patients following HLT. A transient early postoperative biochemical abnormality was noted in 12 patients, and 16 have persisting biochemical abnormalities with no clinical symptoms. Eighteen patients had elevated serum alkaline phosphatase preoperatively, but other liver enzymes were normal. The biochemical abnormality persisted in 11 patients, progressed in five with no clinical symptoms, and was associated with global deterioration in two, who died from unrelated causes. Six patients had globally abnormal liver function tests preoperatively, but none developed clinical hepatic problems postoperatively; five of these patients remain alive, and one died of an unrelated cause. Three patients had undergone combined heart-lung and liver transplantation on account of end-stage liver failure at the time of their initial assessment. One patient is alive and well with normal respiratory and hepatic function 3.5 yrs after surgery, and two patients died (one from donor organ dysfunction and one from multorgan failure in the perioperative period).

**Survival.** The actuarial survival for the group as a whole was 69% to 1 yr, 52% to 2 yrs and 49% to 3 yr [10]. Twenty three patients had one or more possible high risk

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**Fig. 1.** Probability of survival without obliterative bronchiolitis following heart-lung transplantation for cystic fibrosis.
factors, which included preoperative ventilation in 12 patients (six conventional ventilation, five nasal ventilation, one conventional ventilation with extracorporeal membrane oxygenation), previous thoracic surgery in 10 (five ablation pleurectomy (one bilateral), one double-lung transplantation, three thoracotomy (one bilateral), one pleurectomy), chemical pleurectomy in two (one bilateral), and combined heart-lung-liver transplantation for liver failure in three [10]. The actuarial survival at 1 and 2 yrs for patients at high risk was 64 and 57%, respectively, compared to 71 and 49% at 1 and 2 yrs, respectively, for patients in the low risk group [10]. The difference between both groups was significant to three months (p<0.05) but, thereafter, there were no statistically significant differences between the groups. We believe that this finding relates to bleeding, infection, and multiorgan failure, which were more common in the high risk group during the early postoperative period. Eight of the 12 ventilated patients, one of the three patients who had received heart-lung transplantation, five of the 10 patients who had had previous thoracic surgery, and one of the two patients who had had previous chemical pleurectomy survived [10].

Seventeen patients had diabetes mellitus, with a survival of 62% to 1 yr, and 51% to 2 yrs [10]. There were 31 deaths which were due to infection (11), multiorgan failure (8), haemorrhage (6), cerebrovascular accident (2), obliterative bronchiolitis (2), anastomotic dehiscence (1), and hyperacute rejection (1) [10].

Of the surviving patients, only two had never experienced an acute rejection episode. One of these had *P. aeruginosa* and methicillin-resistant *Staphylococcus aureus* in her sputum for the first postoperative month, which cleared with treatment. The second had infection with *P. aeruginosa*, CMV and Mycoplasma pneumoniae during the first three postoperative months, which responded to treatment. Thereafter, neither patient had any further problems. Thus, even after successful surgery, all patients developed at least one serious medical problem.

**Programme of long-term care**

Following discharge from hospital, patients are managed by our unit in collaboration with the referring CF centre. Each patient receives a home micropressor on discharge, and measures FEV$_1$ and FVC on a daily basis. They are advised to contact our unit if there is a greater than 15% reduction in lung function on home testing on two consecutive days, or if they develop a cough, pyrexia in excess of 37.5°C or reduction in exercise tolerance. Patients are initially required to attend outpatient clinics on a weekly basis during the first month after discharge. Thereafter, the frequency decreases, and eventually the majority of patients attend for review every six months. In between, they attend their local hospital for estimates of routine biochemical and haematological indices, together with cyclosporin A level and lung function testing. The results are faxed to Harefield Hospital, and any changes in immunosuppression are made in the light of results of these investigations. Cardiac catheterization is performed on a yearly basis, to monitor patients for the development of accelerated coronary atherosclerosis. However, to date, only one of our patients has experienced this complication at 4 yrs.

Cystic fibrosis patients receive life-long colistin sulphate by nebulizer via a face mask each day, and are advised to perform daily postural drainage if they have any sputum.

The referring centre is encouraged to play an active role in the management of the CF patient following HLT and, indeed, should patients develop problems, the majority will present to their local centre. In such situations, early communication and, if necessary, prompt referral to the transplant centre is essential.

**Discussion**

The medium-term results of HLT for CF are encouraging, with marked improvement in lung function and good rehabilitation. Problems of malabsorption, diabetes mellitus, infection of the upper airways, and salt loss have been successfully managed, and survival of patients with CF is as good as any other group of patients treated by HLT in our unit [11]. The higher doses of cyclosporin required increase the cost [12], although the cost for transplantation may not be high when compared to the cost of looking after a chronically sick patient with CF requiring frequent hospital admissions and intravenous antibiotics. Furthermore, the quality of life is much better for the successfully transplanted patient [13].

It is most important during the early postoperative period to achieve adequate CSA levels as soon as possible, while maintaining good renal function, as failure to do so may increase the frequency and severity of acute rejection episodes and, furthermore, may increase the likelihood of developing obliterative bronchiolitis. Early extubation following HLT is the aim, so as to minimize the incidence of infection in the transplanted lung from *P. aeruginosa* still colonizing the upper airways.

It is important to maximise calorie intake as early as possible. Ideally, this is via the enteral route either orally, nasogastrically or via a gastrostomy feeding tube. Elemental diet is preferred, with calorie supplementation in the form of added carbohydrate and medium chain triglycerides. If patients are diabetic, we continue to give a high calorie intake, and control blood sugar levels with insulin as appropriate. If patients are unable to tolerate enteral feeding (e.g. on account of delayed gastric emptying secondary to temporary vagus nerve neuropraxia) total parenteral nutrition (TPN) may be required. Enteral feeding is used as soon as possible to minimize the risk of infection.

Grand mal seizures were most commonly due to metabolic imbalance. Appropriate measures must be taken to identify and correct any biochemical derangement. Should seizures persist, or if the patient has evidence of focal neurology, a cerebral CT scan is advised, and lumbar puncture may be indicated. Of the 10 patients in the present series who experienced grand mal seizures, two required long-term anticonvulsants.
Episodes of acute rejection and infection were commonly encountered, most frequently during the first three postoperative months. It can be most difficult to differentiate episodes of acute rejection from infection on the basis of clinical findings, appearances of chest radiograph and lung function testing. Serological confirmation of infection takes time. It is, therefore, most important, if in doubt, to perform a fiberoptic bronchoscopy, with bronchoalveolar lavage and transbronchial lung biopsies.

Obliterative bronchiolitis remains a serious problem. It is hoped that by optimizing immunosuppression in the early postoperative period, by rapidly and reliably diagnosing and treating episodes of acute rejection and pulmonary infection, and by the utilization of home spirometers by patients to monitor their lung function, the incidence of this condition will be reduced.

The medium-term results of HLT for CF are encouraging, with marked improvement in lung function and quality of life. It is hoped that further modifications in surgical technique (such as direct revascularization of the bronchial arteries using the internal mammary artery [11]) and medical care will further improve results.

Acknowledgements: The authors would like to thank M. Rehahn for statistical advice, the Cystic Fibrosis Research Trust for financial support for BM, S. Hockley for typing the manuscript and Sir J.C. Batten KVCO for help and encouragement during development of the transplant programme.

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