Outcomes of lung transplantation for cystic fibrosis in a large UK cohort


ABSTRACT
Background: Lung transplantation is an important option to treat patients with advanced cystic fibrosis (CF) lung disease. The outcomes of a large UK cohort of CF lung transplantation recipients is reported.

Methods: Retrospective review of case notes and transplantation databases.

Results: 176 patients with CF underwent lung transplantation at our centre. The majority (168) had bilateral sequential lung transplantation. Median age at transplantation was 26 years. Diabetes was common pre-transplantation (40%). Polymicrobial infection was common in individual recipients. A diverse range of pathogens were encountered, including the Burkholderia cepacia complex (BCC). The bronchial anastomotic complication rate was 2%. Pulmonary function (forced expiratory volume in 1 s % predicted) improved from a pretransplantation median of 0.8 l (21% predicted) to 2.95 l (78% predicted) at 1 year following transplantation. We noted an acute rejection rate of 41% within the first month. Our survival values were 82% survival at 1 year, 70% at 3 years, 62% at 5 years and 51% at 10 years. Patients with BCC infection had poorer outcomes and represented the majority of those who had a septic death. Data are presented on those free from these infections. Bronchiolitis obliterans syndrome (BOS) and sepsis were common causes of death. Freedom from BOS was 74% at 5 years and 38% at 10 years. Biochemical evidence of renal dysfunction was common although renal replacement was infrequently required (<5%).

Conclusion: Lung transplantation is an important therapeutic option in patients with CF even in those with more complex microbiology. Good functional outcomes are noted although transplantation associated morbidities accrue with time.

To date, lung transplantation is the most intensive therapeutic intervention used in the modern management of cystic fibrosis (CF). It remains the only therapeutic option that can restore patients with advanced cystic fibrosis lung disease towards normal respiratory health. Bilateral (sequential) cadaveric donor transplantation is currently the procedure of choice based on international data. As lung transplantation does not alter extrapulmonary manifestations of CF, the burden of comorbidities related to the underlying CF are important considerations in long term survivors.

We were interested in assessing not only simple survival outcomes at our centre but also in defining functional outcomes, obliterative bronchiolitis rates and other major transplant associated comorbidities, such as renal dysfunction and malignancy rates. Hence our aim was to assess outcomes, including survival, and also the prevalence of transplantation associated comorbidities.

METHODS
A retrospective analysis of case notes, clinical charts and transplantation databases from the Freeman Hospital Cardiopulmonary Transplantation Unit was performed.

Case finding and definitions
We performed a retrospective analysis of case notes and the pulmonary transplantation database at our institution from 1989 (programme start) to the present date. We assessed all recipients with CF, including adult and paediatric cases, undergoing pulmonary transplantation, and reviewed their case notes and microbiological results. We have a comprehensive database of recipients with CF transplanted at our institution and cross referenced this with laboratory records to ensure the complete cohort was considered.

Peritransplantation management
We used a 5 day induction protocol with anti-thymocyte globulin (titrated by flow cytometric analysis of peripheral blood T lymphocytes) and intravenous methylprednisolone (2 mg/kg). All patients had triple immunosuppression post-transplantation comprising ciclosporin, prednisolone and azathioprine. Ciclosporin was commenced immediately post-transplantation if renal function was satisfactory. Alternative agents were used in the context of an international clinical trial (mycophenolate) or where intolerance of ciclosporin was noted (tacrolimus). Up to 5 days of intravenous ciclosporin was given in view of poor absorption of ciclosporin in CF. Prophylactic antibiotics were given to the recipient tailored to the most recent sensitivities derived from sputum cultures. If the isolate was panresistant, or recent information was unavailable, 2 g of aztreonam 8 hourly for 2–7 days was used. More recently, multiple antibiotic synergy testing has been incorporated into our microbiological workup of...
Survival analysis and causes of death recording
Survival data are routinely collected as part of the national transplant surveillance programme. Actuarial survival analysis was conducted using Stata software V.4.5. The causes of deaths following transplantation were recorded from the notes. If there were doubts to the cause of death in the absence of a post mortem examination, two or more investigators reviewed the notes and a cause of death attributed based on supporting evidence in the notes. Sepsis related deaths were recorded where a pathogen was identified clinically and microbiologically as causal to the recipient’s terminal decline or where a clinical diagnosis of infection was made and other possible diagnoses were excluded.

Renal disease/dialysis requirements
Although radioisotope measurement of renal function using chromium EDTA-glomerular filtration rate (GFR) forms part of the pretransplantation assessment, we do not use this technique to follow-up patients post-transplantation. Renal function was determined by serial serum creatinine levels recorded pretransplantation, at each routine clinic visit, including 1 year after transplantation, at 5 years and at 10 years. The number of patients receiving renal replacement therapy or who had undergone secondary renal transplantation was recorded from the case notes.

Microbiology
Peritransplantation microbiology from sputum and BAL of the recipient lung on the day of transplantation was recorded from the case notes/microbiology database. The presence or absence of bacterial colonisation based on microbial culture and the commercial phenotyping system API-20NE (Biomerieux, L’Etoile, France) species designation was recorded. Pulsed field gel electrophoresis assessment of microbiological clonality was not routinely conducted. Multiresistance and panresistance characteristics of Pseudomonas aeruginosa were recorded using previous definitions.

Malignancy
Solid organ or haematological malignancy rates were identified from patient case notes and from cross referencing with

![Figure 1](http://thorax.bmj.com/)

**Figure 1** Actuarial survival of patients with cystic fibrosis (CF) at the Freeman Hospital Lung Transplant Programme compared with all other sequential single lung transplants performed. Solid line represents actuarial survival for the CF recipients receiving bilateral sequential single lung transplants (BSLTx); broken line represents all other BSLTx performed at our centre (n = 100). No significant difference in survival was found between the cohorts (log rank testing; Mantel–Cox, p = 0.29).

Cystic fibrosis
such patients using a previously described method. Aminoglycoside antibiotics were avoided in view of the potential synergistic toxicity with ciclosporin and loop diuretics. Patients were given an antistaphylococcal agent, flucloxacinil or clindamycin, in addition to metronidazole. We used prophylactic nebulised amphotericin or oral itraconazole/voriconazole in patients who had evidence of pretransplantation Aspergillus infection with positive sputum cultures for this pathogen.

Operative interventions
These were performed as follows: heart–lung transplantation was performed via sternotomy with tracheal anastomosis and bicaval anastomosis. Bilateral (segmental) lung transplantation from a cadaveric donor was performed via clamshell incision with hilar anastomoses. In all cases the bronchial anastomosis was done with a mixture of continuous and interrupted monofilament nylon. Care was taken to place the anastomosis as close as possible to the lung parenchyma, no further than one cartilaginous ring from the bifurcation of the main bronchus. All bilateral lung transplants were done with cardiopulmonary bypass. In some cases, bypass was used only during implant of the second lung, but both lungs were reperfused simultaneously. No procedures in this series were done without bypass. Aprotinin was used routinely. Living related lobar donor transplantation was also performed via clamshell incisions.

Surveillance associated complications
We routinely perform surveillance transbronchial biopsies and bronchoalveolar lavage at 1 week, 1 month, 3 months, 6 months and 1 year post-transplantation and at any time of unexplained deterioration. Major complications of transbronchial biopsy were recorded as present if there was requirement for chest drain insertion, biopsy associated bleeding with requirement for invasive ventilation or death following a procedure.

Airway complications
All our recipients underwent bronchoscopic and respiratory physiology assessment and monitoring for anastomotic complications. Airway complications such as stenosis, dehiscence and need for stenting were recorded from the case notes. Significant stenosis was deemed present if dilatation, stenting or debridement were required.

Obliterative bronchiolitis
Pulmonary function tests were performed according to accepted guidelines. Forced expiratory volume in 1 s (FEV1) was performed on a Sensor Medics Autobox 6200 (Sensor Medics Corp, California, USA). The best consecutive FEV1 attained as directed by the guidelines was used to set thresholds for BOS 1 (FEV1 <60% of best recorded post-transplantation FEV1), BOS 2 (FEV1 51–65%) and BOS 3 (FEV1 <50%). The more recently introduced category BOS 0-p was not recorded (see discussion). We used “freedom from BOS” to define patients who failed to demonstrate a fall in FEV1 to the threshold used for BOS 1 or higher. If a patient underwent retransplantation, BOS rates were calculated until retransplantation, then further BOS analysis was based on standard criteria from the date of retransplantation.

生存分析及死亡原因记录
生存数据被定期收集作为国家移植监督计划的一部分。使用Stata软件V.4.5进行了生存分析。死亡原因从病历中记录。如果没有尸检，两个或更多调查者会根据支持证据在病历中分配一个死亡原因。如果怀疑是由于感染而死亡，则会在病历中记录相应的死亡原因。

肾病/透析要求
虽然放射性标记的肾功能（铬EDTA-肾小球滤过率）在术前评估中作为标准方法用于评估肾功能，但对该技术的使用不适用于术后随访。肾功能是通过术后的血清肌酐水平来评估的，该评估包括术后1年，5年和10年。记录了接受透析治疗的患者以及那些接受二次肾移植的患者。

微生物
术前的微生物学从痰液和BAL的移植受者肺部的取样进行，特别是在术日。Pseudomonas aeruginosa的多药耐药性和泛耐药性特性被使用了之前的定义。

恶性
器官或血液学恶性疾病发病率被从病例报告表和从交叉参考中确定。

图1 表示了囊性纤维化（CF）患者在Freeman医院移植项目中的实际生存率与所有其他顺序单肺移植手术的患者的生存率进行比较。实线代表CF受者接受双侧顺序单肺移植手术（BSLTx）的生存率；虚线代表在我们中心（n = 100）所进行的其他BSLTx手术的生存率。生存率没有在两个群体间发现显著差异（log rank测试；Mantel–Cox，p = 0.29）。

囊性纤维症
对于使用了之前已描述方法的患者，使用氨基糖苷类抗生素存在潜在的协同毒性与环孢素和袢利尿剂。患者接受抗葡萄球菌药物，如flucloxacinil或clindamycin，以及metronidazole作为预防性治疗。我们使用了吸入性amphotericin或itraconazole/voriconazole，对于有预移植期Aspergillus感染及阳性痰液培养的患者。

手术干预
这些干预措施如下：心肺联合移植通过正中切口、支气管和上腔静脉进行吻合。在所有情况下，肺移植使用的是带支气管吻合的横向切口。所有双肺移植均使用心肺旁路。在某些情况下，只有在植入第二肺后才使用旁路，但两侧肺都被同时复灌。没有一种程序在无旁路的情况下进行。Aprotinin被常规用于该系列。活体相关大体肺供者移植也在横向切口中进行。

监测相关的并发症
我们常规进行术前支气管镜活检和支气管肺泡灌洗术，分别在术后的第1周、第1月、第3月、第6月和第1年以及出现任何未解明恶化时。主要支气管活检并发症被界定为一旦需要胸腔引流、活检后出血，或要求机械通气或死亡，即满足条件。显著的支气管狭窄被界定为需要支气管扩张、支气管活检后出血，或要求机械通气或死亡。

气道并发症
所有的受者都接受了支气管镜和呼吸生理学评估及监测以检测气道吻合口并发症。气道并发症如狭窄、脱位和需要置入支架被记录于病历中。显著的狭窄被界定为需要支气管扩张、支架活检后出血，或要求机械通气或死亡。

阻塞性支气管炎
肺功能测试根据接受者指南进行。在Sensor Medics Autobox 6200（Sensor Medics Corp，加利福尼亚，美国）上对FEV1进行了测量。根据接受者指南定义的最佳连续FEV1被用于设置BOS 1（FEV1 <60%的术前最佳记录FEV1）、BOS 2（FEV1 51–65%）和BOS 3（FEV1 <50%）。最近引入的BOS 0-p category未被记录（见讨论）。我们使用“无BOS”来定义那些未达到所使用的BOS 1或更高的受者。如果患者接受再移植，则BOS在再移植前计算，之后的BOS分析基于标准的日期。

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Pretransplantation morbidity

Significant pretransplantation morbidity was noted within this group; 71 patients (40%) had pretransplantation diabetes mellitus, the majority of whom were treated with insulin therapy. A further 55 patients (20% of cohort) developed diabetes following transplantation, leaving 61 (35%) at follow-up with normal serum glucose levels and normal HbA1c levels, with 5% of patients awaiting annual assessment. The majority of patients developing post-transplantation diabetes were established on insulin therapy (31/35). In those who developed diabetes following transplantation, 31 patients were maintained on tacrolimus at the time of our assessment and four remained on ciclosporin.

RESULTS

Lung transplantation commenced at this institution in 1987 with the first transplantation procedure for CF in 1989. The total number of lung transplantation procedures performed at the time of writing was 575 performed for all indications, with 176 lung transplantsations performed in patients with CF (30% of the total lung transplant population). Of these, 167 were adults (age >17 years) and nine were paediatric cases (age <17 years; range 12.5–17). There were 91 female patients and 85 male patients transplanted. Median age at transplantation was 26.2 years (range 12.5–49.5).

The operative interventions were 168 bilateral (sequential) lung transplantsations from cadaveric donors (BSLTx), four heart–lung transplantation procedures, one patient received living related lobar donor transplantation and in two cases single lung transplantation. One patient underwent BSLTx and combined liver transplantation. Additionally, one CF recipient who had previously undergone BSLTx had “re-do” single lung transplantation performed for acute respiratory failure requiring intubation and mechanical ventilation. This patient died after the re-do transplant within 30 days, and as a result we no longer retransplant patients who are inversely ventilated. In contrast our experience with re-do transplantation, for other indications transplanted when stable, has a mean survival of more than 2 years.

In those recipients receiving single lung transplantation, one patient had previously had a pneumonectomy and the other had single lung transplantation and contralateral pneumonectomy because of thoracic wall deformity. Nineteen patients had pretransplantation infection with BCC and were grouped together in view of the association with poorer outcomes following transplantation. The outcomes in this group will be discussed in detail elsewhere in terms of microbiology and genomovar related outcomes (in submission).

Table 1 Comparison of published actuarial survival figures for lung transplantation in cystic fibrosis recipients from selected case series

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Newcastle survival data at 1 year (1 y). Newcastle (excluding BCC) represents our transplantation results for CF excluding those with pretransplantation Burkholderia cepacia complex (BCC) infection (includes bilateral sequential single lung transplants and other operative interventions). The actual number of patients surviving at each time point is noted in italics. Data reported elsewhere include Egan and colleagues, Burton and colleagues and Quattrucci and colleagues. Hadjiliadis et al represents survival outcomes in cystic fibrosis recipients with sensitive organisms (sens) and panresistant organisms (PanR).

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n, recipient numbers, NR, not recorded.

oncology services. Minor skin neoplasia rates caused by basal cell carcinoma or superficial squamous cell carcinomas were not actively recorded.

Survival and causes of death

The survival figures for the whole cohort were 82% survival at 1 year, 70% at 3 years, 62% at 5 years and 51% at 10 years. Our survival figures, excluding those patients with pretransplant BCC infection, were 84% survival at 1 year, 70% survival at 5 years, 60% survival at 5 years and 53% at 10 years. We compared our Kaplan–Meier survival rates for the CF cohort with that of bilateral (sequential) lung transplantation for all other transplantation indications at our centre (fig 1, table 1). There was no significant difference noted between survival in CF and non-CF transplantation cohorts (log rank testing; Mantel–Cox, p = 0.29).

There are currently 107 CF lung transplant recipients alive (61% of cohort). Causes of death were not identifiable in all cases. This reflects our wide referral area and shared care with referring centres of post-transplant patients. Three patients died at home or at the referring centre and did not have satisfactory data to confirm the recorded cause of death was correct. We were able to identify 35 cases where obliterative bronchiolitis or BOS was the recorded cause of death, accounting for 51% of all observed deaths (table 2).

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n, recipient numbers, NR, not recorded.
Death caused by sepsis was noted in 18 cases (of these BCC infection was the cause of death in seven cases, Clostridium difficile colitis in two cases, cytomegalovirus infection in two cases, panresistant Pseudomonas aeruginosa in one case and Aspergillus spp in one case). In an additional three cases, a sepsis syndrome was identified as the cause of death although no specific pathogen was isolated. Our current sepsis death rate was therefore 26% of all recorded CF transplantation recipient deaths. Other causes of death were rare (n = 1 unless otherwise stated). These included respiratory failure (n = 2), primary graft dysfunction (n = 2), acute respiratory distress syndrome (n = 2), post-transplant lymphoproliferative disease (n = 1), other malignancies (lung (n = 1) and liver (n = 1)), neurological complications, cardiac arrest, bronchial dehiscence and portal hypertension associated gastrointestinal bleeding.

Pulmonary function and obliterative bronchiolitis
Pulmonary function (FEV₁% predicted) improved from a pretransplantation median of 0.8 l (21% predicted) to 2.95 l at 1 year following transplantation (78% predicted). The median FEV₁ at 5 years post-transplantation was 2.75 l and 2.2 l at 10 years post-transplantation (p<0.01 at each time point compared with pretransplantation values, paired t test). Obliterative bronchiolitis, as defined clinically by BOS status, was BOS 0 (freedom from BOS) in 85% at 1 year, 74% at 5 years and 38% at 10 years (fig 2).

Renal disease
Pretransplantation EDTA-GFR results demonstrated a median GFR of 125 ml/min (range 67–200). Following transplantation, serum creatinine worsened with a mean pretransplant creatinine of 73 mg/dl (range 58–140) rising to 121.5 mg/dl (range 66–235) at 1 year (p<0.001) (fig 3). Estimated GFR (eGFR) data are not available at the time of writing, reflecting our institution’s recent adoption of this measurement. Three patients required haemodialysis (1.1% of the total CF transplant cohort—one patient remains alive). Two patients have undergone secondary renal transplantation (1.1% of total CF transplant cohort—one patient remains alive).

Surveillance associated comorbidities
The majority of patients underwent our standard biopsy protocols resulting in more than 800 transbronchial biopsy procedures performed. No patient died as a consequence of a biopsy procedure. No cases were noted as requiring invasive mechanical ventilation or blood transfusion following a transbronchial biopsy. Reflecting the recently instituted prospective electronic database of biopsy results, we identified 438 biopsies taken within the first year. Acute vascular rejection (International Society for Heart Lung Transplantation (ISHLT) grade A2 or greater) was noted in 77 of 187 biopsies taken within the first month (0–30 days). Thus biopsy data gave an observed first month acute vascular rejection rate of 41%. We identified 32/251 cases of acute rejection from days 30–366 post-transplantation as part of our routine surveillance programme.
This rejection rate equates to 12% of biopsies undertaken between 1 month and 1 year post-transplantation.

**Malignancy**

One patient suffered donor acquired small cell lung carcinoma, as previously reported. Post-transplant lymphoproliferative disease was noted in five patients (2.5% of cohort).

**Microbiology**

Peritransplantation microbiological cultures, including those prior to transplantation and within the first week following transplantation, were achieved in all patients. A large range of pathogens were seen in the cohort and polymicrobial infections in individual recipients were common (fig 4). Infection with more than one *Pseudomonas* strain was assumed in the presence of mucoid and non-mucoid phenotypes and/or widely differing antibiotic sensitivities. Pulsed field gel electrophoresis studies that assess different bacterial lineages were not routinely conducted so our assumption may be incorrect and such bacteria could include some clonal strains with marked morphotypic/phenotypic variation. Noting this caveat, we found 54% of patients appeared to have two or more distinct *Pseudomonas* strains. A further 14% of patients had panresistant *Pseudomonas aeruginosa* infections and similarly 14% of patients had multiresistant *Pseudomonas aeruginosa* infections. BCC infections were noted in 15%, *Aspergillus* infection in 12%, *Stenotrophomonas* spp infection in 9%, *Alcaligenes* spp infections in 6%, *Scedosporium* spp infections in 2% and methicillin resistant *S aureus* infection (MRSA) in 2%. Atypical mycobacteria were not isolated in our cohort at the time of transplantation although infection with such organisms does not reflect a specific exclusion criterion for transplantation at this centre.

**Airway complications**

In 176 recipients with 346 bronchial anastomoses, we noted four recipients with major anastomotic complications (overall major bronchial anastomotic complication rate 2%). One recipient suffered bronchial dehiscence. Three recipients had anastomotic strictures that required dilatation and stenting.

**DISCUSSION**

Lung transplantation for CF accounts for approximately one-third of all sequential single lung transplants performed at this centre, a distribution similar to that reported by the International Society for Heart Lung Transplantation (ISHLT) registry. Our series of cystic fibrosis lung transplants is one of the largest reported to date and our survival rates are similar to the best of the previously reported series (table 1). The survival rates for CF recipients reported by Egan et al were similar to those at our centre, most procedures were bilateral sequential single lung transplantation, and were 81% at 1 year, 59% at 5 years and 38% at 10 years. Our approach has been predominantly with bilateral sequential single lung transplantation and this compares favourably with that of heart–lung transplantation for CF.

The predominant surgical technique used was bilateral sequential single lung transplantation with cardiopulmonary bypass. Routine use of bypass facilitated a standard technique across a relatively large surgical and anaesthetic team. Both main bronchi were stapled after recipient pneumonectomy, facilitated by the single lumen endotracheal tube which allowed irrigation and removal of contaminated secretions from the (retained) distal airway. We believe this technique reduces intraoperative contamination. Finally, reperfusion of both lungs simultaneously allows close control of pressure and avoids circulatory overload of one lung.

Bronchial anastomotic complications were uncommon, with an overall major bronchial anastomotic complication rate of 2% in comparison with prior reports in CF recipients of up to 7% and 14%. More recently, rates of anastomotic complications in a cohort, including CF and other lung transplantation indications, were 15%. The reasons for our low anastomotic complication rates remain unclear. We did not, however, routinely perform bronchial artery revascularisation (possible protective benefits) nor did we routinely perform telescoping of the bronchial anastomosis (possible promoter of anastomotic complications). We do not however have data on other factors recently implicated in the genesis of anastomotic complications, such as recipient length and donor ventilation times. Despite our low rates of anastomotic complications, one episode was felt to have directly contributed to the recipient’s death.

We noted a high rate of pathogens with potential to complicate the early postoperative period, including panresistant *Pseudomonas aeruginosa*, BCC and *Aspergillus* species. We compared our CF cohort with that of all other bilateral sequential single lung transplants performed at our centre (including non-CF bronchiectasis, sarcoidosis, emphysema) and found no significant differences in survival rates (log rank testing p = 0.29). Confounding variables between CF recipients and non-CF recipients may however include differing recipient ages and comorbidities in these two cohorts.

Most of the early deaths (deaths within the first 30 days) following lung transplantation for CF were felt to be caused by sepsis. We noted that 26% of our CF recipient deaths were a result of sepsis, which is also comparable with or less than that reported from other centres. There were significantly higher mortality rates in those who had preoperative BCC infection where seven of 19 patients died from sepsis (56%). The observed higher risk of death due to sepsis in those with pretransplantation BCC infection confirms that of prior reports demonstrating...
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excessive mortality in BCC infected patients.\textsuperscript{14} \textsuperscript{24} Our full experience of transplantation with BCC infection and genomovar specific outcomes will be discussed elsewhere (in press).

No other organisms were significantly associated with poor transplantation outcomes. In particular, infection with multi- or panresistant \textit{Pseudomonas aeruginosa} had no survival disadvantage, confirming prior findings\textsuperscript{10} \textsuperscript{25} \textsuperscript{26} but in contrast with a more recent publication.\textsuperscript{16} None of our recipients had pretransplantation infection with non-tuberculous mycobacteria. This does not reflect a specific policy of declining to transplant individuals with such infections although we do not transplant those infected with \textit{M abscessus} because of concerns over post-transplantation morbidity.\textsuperscript{27}

We did not prospectively assess the clonal nature of bacterial strains with pulsed field gel electrophoresis and assumed that strains with markedly different antibiograms and morphotypes were unrelated clonally. This phenotypic approach may overestimate the number of distinct species of organisms or strains isolated noted in fig 4.

Pretransplantation comorbidity was common, with significant rates of CF related diabetes, CF related liver disease, prior pneumothorax or chest surgery and weight loss. We do not view CF related liver disease as a contraindication per se although we regularly seek expert assessment for hepatobiliary and liver transplant colleagues. Despite this multidisciplinary approach, one patient died of hepatobiliary complications related to variceal bleeding following transplantation. Low body mass index was noted in selected patients with the lowest recorded pretransplantation body mass index of 12 kg/m\textsuperscript{2}. In general, we prefer to avoid transplanting patients with a body mass index less than 16 kg/m\textsuperscript{2} but may elect to do so if the potential recipient has no other relative contraindications and has made maximal efforts with assisted nutrition. Interestingly, there was no clear association between poor post-transplant survival and prior pneumothorax or prior non-invasive ventilation.

We noted a good functional outcome following transplantation with an increase in FEV\textsubscript{1} at 1 year following transplantation to almost 3 l (78% predicted). Similar to prior reports, we used “freedom from BOS”, as defined by patients who failed to demonstrate a fall in FEV\textsubscript{1} to the criterion used for BOS 1 or higher.\textsuperscript{15} The majority of patients were free from BOS 1 or higher at 1 year (~85%) and 73.6% at 5 years. In those recipients surviving 10 years, 37.5% of patients had freedom from BOS 1. Similar “freedom from BOS” rates in CF recipients have been reported at the Rome transplant programme (95% at 1 year, 82.5% at 2 years, 70% at 3 years and 65% at 5 years).\textsuperscript{9} Earlier reports have demonstrated freedom from BOS as 84% at 1 year and 51% at 3 years.\textsuperscript{13} One possible criticism using “freedom from BOS” and not the newly categorised BOS 0-p is that our study cannot report those at risk of BOS. We were unable to report BOS 0-p because of the large numbers of patients being transplanted prior to the introduction of the new BOS 0-p category where FEV\textsubscript{1} data were unavailable.

Transplantation in our CF cohort was associated with significant post-transplantation comorbidities, in particular renal dysfunction.\textsuperscript{2} In a smaller series previously reported, three patients (11% of the total CF recipients) required dialysis following lung transplantation. In the series of 55 Italian CF recipients reported by Quattrucci and colleagues,\textsuperscript{7} the authors noted that the most common medical complication after transplantation, observed in 27 patients, was chronic renal failure. Our rates of renal dysfunction are therefore lower than those previously reported. This is noteworthy as we now have an aggressive policy in non-rejecters (those with biopsies of grade A1 or less) to reduce target ciclosporin or tacrolimus levels by the end of the first year. Such a strategy may however be ineffective as the majority of nephron loss has been postulated to occur in the first year following transplantation.\textsuperscript{28} While aggressive aminoglycoside antibiotic therapy may stabilise patients with CF on a transplant waiting list, we did not specifically assess if those patients with lower transplant assessment EDTA-GFR recordings had received more courses of these potentially nephrotoxic antibiotics. Irrespective of this, the level of post-transplantation renal dysfunction in this cohort has remained low.

Other important major post-transplantation complications encountered in our cohort have included four recipients who developed fulminant pseudo-membranous colitis where the mortality rate was 50% despite urgent colectomy.\textsuperscript{29} One patient has required a post-transplantation left pneumonectomy related to pulmonary vascular anastomosis compromise associated with mediastinal lymphadenopathy. Post-transplantation bronchoscopy and surveillance associated morbidity was extremely low and had a high detection rate of asymptomatic acute vascular rejection similar to that recently reported.\textsuperscript{30} Many of these rejection episodes were asymptomatic and not associated with an obvious fall in lung function. The surveillance protocols used at our centre have also contributed to our understanding of post-transplantation graft dysfunction offering hope in extending the longevity of both the graft and recipient.\textsuperscript{30} \textsuperscript{31} \textsuperscript{32}

The retrospective nature of our study has, by definition, inherent weaknesses. Many of the deaths were not confirmed by autopsy findings leading to potential incorrect categorisation of the cause of death (eg, BOS may be associated with secondary bacterial infection) and this makes the cause of death difficult to differentiate. Autopsy should be considered where possible if the cause of decline is not clear. Also of note is the lack of prospective data on metabolic bone disease, a common comorbid condition in CF. Although we are unaware of any known osteoporotic fractures, a systematic bone density assessment programme following transplantation was not adopted until recently. Other important areas to be considered for future studies would include employment status, assessments of psychiatric morbidity and quality of life measurements.

Bilateral sequential lung transplantation is a well established treatment for patients with end stage CF associated lung disease. The perioperative mortality is low and recipients with CF have a significant early survival and functional benefit after lung transplantation. Long term results are good, although both transplantation associated comorbidities and increasing rates of graft dysfunction occur with time.

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REFERENCES


Cystic fibrosis

IL6 and dendritic cells in allergic asthma

Interleukin (IL6) production by antigen-presenting dendritic cells (DCs) is integral to the differentiation of T helper cells into T helper type Th1, Th2 and Th17 subsets. However, molecular mechanisms that regulate IL6 production in DCs are yet to be elucidated. Stimulation of bone marrow-derived dendritic cells with the allergen house dust mite (HDM)—which causes asthma in humans—or the mucosal adjuvant cholera toxin promoted cell surface expression of c-Kit and its ligand, stem cell factor (SCF), resulting in sustained signalling downstream of c-Kit, prompting IL6 secretion. DCs from c-Kit mutant mice secreted smaller amounts of IL6 following HDM or cholera toxin stimulation, resulting in an inability to induce a robust Th2 or Th17 response and reduced allergic airway inflammation. In addition, expression of Jagged-2, a Notch ligand which has been associated with Th2 differentiation, is reduced in DCs lacking functional c-Kit, implying that c-Kit upregulates expression of Jagged-2 in addition to IL6. Cell signalling downstream of c-Kit is likely to involve phosphorylation of Akt via activation of phosphatidylinositol-3 kinase (PI3K), as DCs expressing a catalytically inactive form of P13K secrete less IL6 on cholera toxin stimulation.

It is concluded that cell surface expression of c-Kit by DCs in conjunction with SCF causes extended activation of the PI3K-Akt pathway, promoting a higher IL6 expression profile in DCs which, in turn, promotes T cell differentiation towards Th2 and Th17 lineage. This may have implications for the understanding and treatment of allergic airway inflammation in asthma as downregulation of c-Kit may reduce such inflammation. Inhibition of c-Kit may also promote the efficacy of vaccines in cancer therapy by augmenting a Th1 response.


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