Outcomes of Lung transplantation for Cystic Fibrosis in a large United Kingdom cohort


GM and ADS contributed equally to the manuscript

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Keywords Cystic Fibrosis, Pseudomonas aeruginosa, Burkholderia, Lung Transplantation, survival.

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Abstract

**Background** Lung transplantation is an important option to treat patients with advanced Cystic Fibrosis (CF) lung disease. We report the outcomes of a large UK cohort of CF lung transplantation recipients. **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 (FEV1% predicted) improved from pre-transplantation median 0.8 litres (21% predicted) to 2.95 litres (78% predicted) at one year following transplantation. We noted an acute rejection rate of 41% within the first month. Our survival figures were 82% survival at one year, 70% at three years, 62% at five years and 51% at ten years. Patients with BCC infection had poorer outcomes and represented the majority of those who had a septic death. We present data on those free from these infections. Bronchiolitis Obliterans Syndrome (BOS) and sepsis were common causes of death. Freedom from BOS was 74% at five years and 38% at ten years. Biochemical evidence of renal dysfunction was common though renal replacement was infrequently required (<5%). **Interpretation:** 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.
**Introduction**

To date lung transplantation is the most intensive therapeutic intervention used in 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. (1)

Long term morbidity following lung transplantation is well described both relating to obliterative bronchiolitis or bronchiolitis obliterans syndrome (BOS) (1), immunosuppressant toxicity (e.g. renal dysfunction)(2) and secondary malignancy. (1) A number of single centre case series of lung transplantation for cystic fibrosis have been reported and demonstrate in general excellent post transplant survival results. (3-6)

As lung transplantation does not alter extra-pulmonary manifestations of CF the burden of co-morbidities related to the underlying CF are important considerations in long term survivors.

We were interested to assess not only simple survival outcomes at our centre but to also define functional outcomes, obliterative bronchiolitis rates and other major transplant associated co-morbidities such as renal dysfunction and malignancy rates.
Aims

We sought to assess outcomes including survival and also the prevalence of transplantation associated co-morbidities.

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 (program start) to the present date. We assessed all recipients with Cystic Fibrosis (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.

Peri-transplantation management

We used a 3-day induction protocol with anti-thymocyte globulin (titrated by flow cytometric analysis of peripheral blood T-lymphocytes) and intravenous methylprednisolone (2mg/kg). All patients had triple immunosuppression post-transplantation comprising ciclosporin, prednisolone and azathioprin. 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 five
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 pan-resistant, or recent information was unavailable, 2g aztreonam 8 hourly for 2-7 days was used. More recently multiple antibiotic synergy testing has been incorporated into our microbiological work up of such patients using a previously described method.(7, 8) Aminoglycoside antibiotics were avoided in view of the potential synergistic toxicity with ciclosporin and loop diuretics. Patients were given an anti-staphylococcal agent, flucloxacillin or clindamycin, in addition to metronidazole. We used prophylactic nebulised amphotericin or oral itraconazole / voriconazole in patients who had evidence of pre-transplantation 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 bicaival anastomosis. Bilateral (sequential) 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 mono-filament 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 transplantations 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 patients 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 case notes. Significant stenosis was deemed present if dilatation, stenting or debridement were required.(6)

**Obliterative bronchiolitis**

Pulmonary function tests were performed according to accepted guidelines. The Forced Expiratory Volume in 1 second (FEV1) was performed on a Sensor Medics Autobox 6200 (Sensor Medics Corp. California, U.S.A.). The best consecutive FEV1 attained as directed by guidelines were used to set thresholds for BOS 1 (FEV1 66-80 % of best recorded post transplantation FEV1), BOS 2 (FEV1 51-65%) and BOS 3 (FEV1 <50%). The more recently introduced category BOS-0p 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 bronchiolitis obliterans syndrome BOS 1 or higher (9). If a patient underwent re-transplantation the BOS rates were calculated until re-transplantation, then further BOS analysis was based upon standard criterion from the date of re-transplantation.

**Survival analysis and causes of death recording**
Survival data is routinely collected as part of the national transplant surveillance program. Actuarial survival analysis was conducted using StatView software version 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 radio-isotope measurement of renal function using $^{51}$Chromium EDTA-GFR forms part of pre-transplantation assessment we do not use this technique to follow up patients post-transplantation. Renal function was determined by serial serum creatinine levels recorded pre-transplantation, at each routine clinic visit including one 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 case notes.

**Microbiology**

Peri-transplantation microbiology from sputum and BAL of the recipient lung on the day of transplantation was recorded from case-notes/microbiology database. The presence or absence of bacterial co-infection based on microbial culture and the commercial phenotyping system API-20NE (Biomerieux, L’Etoile, France) species designation was recorded. Pulsed field gel electrophoresis (PFGE) assessment of microbiological clonality was not routinely conducted. Multi-resistance and pan-resistance characteristics of *Pseudomonas aeruginosa* was recorded using previous definitions.(10)
Malignancy

Solid organ or haematological malignancy rates were identified from patient case-notes and from cross-referencing with oncology services. Minor skin neoplasia rates due to basal cell carcinoma or superficial squamous cell carcinomas were not actively recorded.
Results

Lung transplantation commenced at this institution in 1987 with the first transplantation procedure for Cystic Fibrosis in 1989. The total number of lung transplantation procedures performed at time of writing was 575 transplants performed for all indications with 176 lung transplantations performed for Cystic Fibrosis patients (30% of the total lung transplant population). Of these 167 were adults (age greater than 17 years) and nine were paediatric cases (age less than 17; range 12.5-17 years). There were 91 female patients and 85 males transplanted. Median age at transplantation was 26.2 years (range 12.5-49.5 years).

The operative interventions were 168 bilateral (sequential) lung transplantation from cadaveric donors (BSLTx), four heart-lung transplantation procedures, one patient received living related lobar donor transplantation and in two cases single lung transplantation (SLTx). 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 re-transplant patients who are invasively ventilated. In contrast our experience with re-do transplantation, for other indications transplanted when stable, has a mean survival of over 2 years.

In those recipients receiving single lung transplantation, one patient had previously had a pneumonectomy and the other had single lung transplantation and contra-lateral pneumonectomy because of thoracic wall deformity. Nineteen patients had pre-transplantation infection with Burkholderia cepacia complex 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).
Pre-transplantation morbidity

Significant pre-transplantation morbidity was noted within this group; 71 patients (40%) had pre-transplantation diabetes mellitus the majority of whom were treated with insulin therapy. A further 35 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 are established on insulin therapy (31/35). In those who developed diabetes following transplantation thirty-one patients were maintained on tacrolimus at time of our assessment and four remained on ciclosporin A.

As previously reported pleural disease was also common.(12) We noted 21 patients (12%) with a previous pneumothorax. The pre-transplantation management by referring teams included intercostal chest drain in 11 patients, medical pleurodesis in four patients and thoracic surgical pleurodesis in two patients. Survival outcomes were not worsened in those with previous pneumothorax (Mantel-Cox log rank testing p=0.78).(12) An additional patient had undergone upper lobectomy prior to transplant listing. Previous non-invasive ventilation had been used in 22 patients (12% of the cohort). Prior non-invasive ventilation was not associated with a poorer prognosis as compared to the rest of the CF cohort (Mantel-Cox log rank testing p=0.89). Percutaneous entero-gastrostomy (PEG) was present in 23 recipients (13%) pre-transplantation and overnight nasogastric feeding in 10 recipients (6%). The median body mass index was 18.6 kg/m² pre-transplantation (range 12-26) and this increased at 1 year to a median of 20.3 kg/m².

Survival and causes of death

The survival figures for the whole cohort were 82% survival at one year, 70% at three years, 62% at five years and 51% at ten years. Our survival figures excluding those patients with pre-transplant *Burkholderia cepacia* complex infection were 84% survival at one year, 70%
survival at three years, 60% survival at five years, and 53% at ten years. We compared our Kaplan-Meier survival rates for the CF cohort to that of bilateral (sequential) lung transplantation for all other transplantation indications at our centre (Error! Reference source not found.). 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).

Death due to sepsis was noted in 18 cases (of these Burkholderia cepacia complex infection was the cause of death in seven cases, Clostridium difficile colitis in two cases, Cytomegalovirus infection in two cases, pan-resistant Pseudomonas aeruginosa in one case and Aspergillus infection in one case). In an additional three cases a sepsis syndrome was identified as the cause of death though no specific pathogen 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 (PTLD) (n=1), other malignancies; lung (n=1) and liver (=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 pre-transplantation median of 0.8 litres (21% predicted) to 2.95 litres at 1 year following transplantation (78% predicted). The median FEV1 at 5 years post-transplantation was 2.75 litres and 2.2 litres at ten years post transplantation (p<0.01 at each time point compared to pre-transplantation values, paired t-test). Obliterative bronchiolitis as defined clinically by Bronchiolitis Obliterans Syndrome (BOS) status was BOS 0 (freedom from BOS) (9) in 85% at 1 year, 74% at five years and 38 % at ten years (figure 2).

**Renal disease**

Pre-transplantation EDTA-GFR results demonstrated a median GFR of 125ml/min (range 67-200). Following transplantation serum creatinine worsened with a mean pre-transplant creatinine 73mg/dl (range 33-140mg/dl) rising to 121.5 mg/dl (range 66-235mg/dl) at one year (p<0.001) (Error! Reference source not found.). Estimated GFR (eGFR) data are not available at time of writing reflecting our institutions’ recent adoption of this measurement. Three patients have 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 co-morbidities**

The majority of patients underwent our standard biopsy protocols resulting in over 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 data basing of biopsy results we identified 438 biopsies taken within the first year. Acute vascular rejection (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 day 30-366 post transplantation as part of our routine surveillance program. 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.(13) Post transplant lympho-proliferative disease (PTLD) was noted in five patients (2.8% of cohort).

**Microbiology**

Peri-transplantation 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 (Error! Reference source not found.). 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 (PFGE) 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 pan-resistant *Pseudomonas aeruginosa* infections and similarly 14% of patients had multi-resistant *Pseudomonas aeruginosa* infections. *Burkholderia cepacia* complex 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 though infection with such organisms does not reflect a specific exclusion criteria 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 Cystic Fibrosis 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.\(^{(1)}\) 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.\(^{(10, 14-16)}\) The survival rates for CF recipients reported by Egan \textit{et al} where similar to our centre, most procedures were bilateral sequential single lung transplantation, were 81\% at 1 year, 59\% at 5 years, and 38\% at 10 years.\(^{(17)}\) Our approach has been predominantly with bilateral sequential single lung transplantation and this compares favourably with that of heart-lung transplantation for cystic fibrosis.\(^{(18)}\)

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 intra-operative 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 to prior reports in CF recipients of up to 7\% and 14\%.\(^{(24, 25)}\) More recently rates of anastomotic complications in a cohort including CF and other lung transplantation indications were 15\%.\(^{(26)}\) The reasons for our low anastomotic complication rates remain unclear. We did
not, however, routinely perform bronchial artery revascularisation (possible protective benefits)(27, 28) nor did we routinely perform telescoping of the bronchial anastomosis (possible promoter of anastomotic complications).(26) 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.(26) 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 post-operative period including pan-resistant *Pseudomonas aeruginosa*, *Burkholderia cepacia* complex and *Aspergillus* species. We compared our CF cohort to that of all other bilateral sequential 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 co-morbidities in these two cohorts.

Most of the early deaths (deaths within the first 30 days) following lung transplantation for CF were felt due to sepsis. We noted 26% of our CF recipient deaths were due to sepsis, which is also comparable to or less than that reported from other centres.(6, 14) There were significantly higher mortality rates in those who had pre-operative *B. cepacia* complex (BCC) infection where 7 of 19 patients died due to sepsis (36%). The observed higher risk of death due to sepsis in those with pre-transplantation BCC infection confirms that of prior reports demonstrating excessive mortality in BCC infected patients.(14, 19) Our full experience of transplantation with *Burkholderia cepacia* complex 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 pan-resistant *Pseudomonas aeruginosa* had no survival disadvantage confirming prior findings (10, 20, 21) but in contrast to a more recent publication (16). None of our recipients had pre-transplantation infection with non-Tuberculous Mycobacteria (NTM). This does not reflect a specific policy of declining to transplant individuals with such infections although we do not transplant those infected with *M. abscessus* due to concerns over post-transplantation morbidity. (22)

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 over-estimate the number of distinct species of organisms or strains isolated noted in Figure 4.

Pre-transplantation co-morbidity 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* though we regularly seek expert assessment 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 pre-transplantation BMI of 12kg/m\(^2\). In general we prefer to avoid transplanting patients with a BMI less than 16kg/m\(^2\) but may elect to do so if the potential recipient has no other relative contra-indications 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 FEV1 at one year following transplantation to almost 3 litres (78% predicted). Similar to
prior reports we used “freedom from BOS” as defined by patients who failed to demonstrate a fall in FEV1 to the criterion used for bronchiolitis obliterans syndrome BOS 1 or higher.(15) The majority of patients were free from BOS 1 or higher at one year (~85%) and 73.6% at 5 years. In those recipients surviving ten years 37.5% of patients had freedom from BOS 1. Similar “freedom from bronchiolitis obliterans syndrome” rates in CF recipients have been reported at the Rome transplant program as 95% at one year, 82.5% at two years, 70% at three years, and 65% at five years.(9) Earlier reports have demonstrated freedom from bronchiolitis obliterans syndrome as 84% at 1 year and 51% at 3 years.(15) 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 due to the large numbers of patients being transplanted prior to the introduction of the new BOS 0-p category where FEF25-75 data was unavailable.

Transplantation in our CF cohort was associated with significant post-transplantation co-morbidities, in particular, renal dysfunction.(2) In a smaller series previously reported three patients (11% of total CF recipients) required dialysis following lung transplantation. In the series of 55 Italian CF recipients reported by Quattrucci et al (9) 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 all 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.(23) Whilst 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.(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, had a high detection rate of asymptomatic acute vascular rejection similar to that recently reported.(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.(31-33)

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 for example 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 co-morbid 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 peri-operative 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 co-morbidities and increasing rates of graft dysfunction occur with time.
References


8. Lang BJ, Aaron SD, Ferris W, Hebert PC, MacDonald NE. Multiple combination bactericidal antibiotic testing for patients with cystic fibrosis infected with multiresistant strains


Table 1 Comparison of Published Actuarial Survival Figures for Lung Transplantation in Cystic Fibrosis recipients from selected case series

Key; Newcastle survival data at one year (1 yr). NR represents not recorded, n= represents recipient numbers, Newcastle (excluding BCC) represents our transplantation results for Cystic Fibrosis excluding those with pre transplantation *Burkholderia cepacia* complex infection (includes BSLTx and other operative interventions). The actual number of patients surviving at each time point is noted in italics. Data reported elsewhere includes Egan *et al* (see reference (17), Burton *et al* (5), Quatrucci *et al* (9). Hadjiliadis *et al* represents survival outcomes in CF recipients with sensitive organisms (sens) and pan-resistant organisms (PanR) (16).

<table>
<thead>
<tr>
<th></th>
<th>Newcastle</th>
<th>Newcastle (excl. BCC)</th>
<th>Egan <em>et al</em></th>
<th>Burton <em>et al</em></th>
<th>Quatrucci <em>et al</em></th>
<th>Hadjiliadis <em>et al</em> (sens)</th>
<th>Hadjiliadis <em>et al</em> (PanR)</th>
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<td>81</td>
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<td>NR</td>
<td>80</td>
<td>70</td>
<td>91</td>
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<td>5 yr</td>
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<td>62 (63)</td>
<td>59</td>
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<td>58</td>
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<td>8 yr</td>
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<td>56 (33)</td>
<td>NR</td>
<td>70</td>
<td>NR</td>
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<tr>
<td>10 yr</td>
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<td>53 (19)</td>
<td>38</td>
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<td>123</td>
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Table 2 Causes of Death in Cystic Fibrosis recipients transplanted at the Freeman Hospital Transplant Programme.

Key; Causes of death in recipients were recorded from case notes. Data is expressed as percentage of all deaths observed in this cohort. Thirty five cases of obliterative bronchiolitis were identified and this accounted for 51% of all deaths in the cohort. The percentages have been rounded up or down to the 1st decimal place.

<table>
<thead>
<tr>
<th>Cause of Death</th>
<th>Number of patients</th>
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<tbody>
<tr>
<td>Obliterative Bronchiolitis</td>
<td>35 (51%)</td>
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<tr>
<td>Infection</td>
<td>18 (26%)</td>
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<td><em>B. cepacia complex</em></td>
<td>7 (10%)</td>
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<tr>
<td><em>Cytomegalovirus</em></td>
<td>2 (3%)</td>
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<tr>
<td><em>C. difficile</em></td>
<td>2 (3%)</td>
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<tr>
<td><em>Aspergillus spp.</em></td>
<td>1 (1.5%)</td>
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<tr>
<td><em>Ps. aeruginosa</em></td>
<td>1 (1.5%)</td>
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<tr>
<td><em>Unknown</em></td>
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<tr>
<td>Malignancy</td>
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<tr>
<td>Acute Resp Distress Syndrome</td>
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<tr>
<td>Graft dysfunction</td>
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<tr>
<td>Gastrointestinal bleed</td>
<td>1 (1.5%)</td>
</tr>
<tr>
<td>PTLD</td>
<td>1 (1.5%)</td>
</tr>
<tr>
<td>Cardiac arrest</td>
<td>1 (1.5%)</td>
</tr>
<tr>
<td>Bronchial dehiscence</td>
<td>1 (1.5%)</td>
</tr>
<tr>
<td>Neurological complications</td>
<td>1 (1.5%)</td>
</tr>
<tr>
<td>Unknown</td>
<td>3 (4.5%)</td>
</tr>
<tr>
<td><strong>Total Number of Deaths</strong></td>
<td><strong>69 (100%)</strong></td>
</tr>
</tbody>
</table>
Figure 1 Actuarial Survival of Cystic Fibrosis patients at the Freeman Hospital Lung Transplant Programme as compared to all other sequential single lung transplants performed.

Key Solid line represents actuarial survival for the Cystic Fibrosis recipients receiving bilateral sequential single lung transplants (BSLTX), Dashed 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).
Figure 1 Rates of Bronchiolitis Obliterans Syndrome (BOS) in Cystic Fibrosis recipients.

Key to Figure 1

Freedom from Bronchiolitis Obliterans Syndrome (BOS) at 1 year (n=134), 5 years (n=63) and 10 years (n=19) following transplantation. Key striped bars - CF recipients with BOS grade 1 or higher, Solid bars - CF recipients who had “freedom from BOS”, Open Bars - patients where data was not available.
Figure 1 Change in serum creatinine (mg/dl) following transplantation.

Key Solid line- median creatinine level observed. Dashed lines represent the 25\textsuperscript{th} and 75\textsuperscript{th} Centile creatinine levels.
Figure 4 Microbial infections prior to transplantation

- >2 Pseudomonas Species
- Multi-R Pseudomonas
- Pan-R Pseudomonas
- Burkholderia cepacia complex
- Aspergillus
- Stenotrophomonas
- Alcaligenes
- Scedosporium
- MRSA