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Chapter

# Lung Transplantation in Patients with Cystic Fibrosis

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## Abstract

Cystic fibrosis (CF) is one of the most common indications for lung transplant (LTx) and nearly one-third of the LTx worldwide are performed in people with CF (PwCF). Due to vast developments in diagnostic modalities, antibiotic therapies, and management of associated comorbidities in dedicated and experienced centres, over the past few decades, more PwCF are reaching adulthood than ever before. This has increased the burden on transplant programs particularly in a universal donor shortage scenario. To improve the donor pool a diligent and proactive donor care management, acceptance of marginal organs and utilisation of ex-vivo lung perfusion systems for organ preservation, assessment, and improvement is being advocated widely. LTx is not a readily available therapy and the average waiting time is 18 months in the UK. Therefore, it is essential that PwCF are referred for LTx assessment when their disease is stable, before respiratory deterioration leads to overall deconditioning of the patients. Once listed for LTx, it is crucial to control waiting list mortality by prioritising rapidly deteriorating patients through schemes like the lung allocation score, national urgent and super-urgent waiting lists, and institutional highlighting of deteriorating patients that do not meet other urgent criteria. LTx in PwCF is challenging due to colonisation of the respiratory tract with multi-drug resistant organisms, associated comorbidities such as diabetes, liver disease, gastro-oesophageal reflux, and distal intestinal obstruction syndrome (DIOS) and CF-specific technical difficulties (adhesions due to prior pneumothoraces or pleurodesis, or bronchial collaterals that increase surgical time). Hilar lymphadenopathy and bronchial collaterals may increase surgical time, organ ischemia time, intra and post-operative bleeding, and blood transfusions. Advances in immunosuppression, prophylactic anti-viral and anti-fungal therapies, early ambulation and rigorous physiotherapy, and meticulous postoperative follow up with spirometry, x-rays, and bronchoscopies to detect rejection at the early stage followed by its efficient treatment have helped to improve post-LTx survival in the CF patients. Constant development in the surgical field with adoption of off-pump transplantation, sternal sparing bilateral thoracotomy approach, and utilisation of mechanical circulatory assist as a bridge to transplant and as a support for primary graft failure strives for better outcomes. However, chronic lung allograft dysfunction, chronic refractory infections, malignancies, and CF associated comorbidities remain major determinants of post-LTx long term survival. Despite this, CF patients are often good candidates for re-do LTx with improving survival outcomes. In this chapter, we are compiling the different aspects of LTx in PwCF emphasising the advances

in bridge to transplantation, the surgical approach, management of primary graft failure, and immunosuppression as well as complications post-transplant.

**Keywords:** cystic fibrosis, lung transplantation, advances,
minimally invasive lung transplantation, off pump lung transplantation

## 1. Introduction

While it took years following the first human LTx in 1963 for this procedure to become a gold standard therapy in the management of end-stage lung disease, the procedure took off in the 80s following the introduction of Cyclosporin in medical practice. The first transplant in a patient with CF was a heart-lung transplant performed by Magdi Yacoub in Harefield Hospital in the United Kingdom [1]. Since then, nearly ten thousand patients with CF have undergone LTx worldwide [2]. According to the 36th adult lung and heart-lung transplant report comprising more than 69000 adult LTx in the ISHLT registry, 15.2% of all adult LTx were performed in PwCF [2]. Although the number of transplants performed for each indication has increased ever since, the proportion of patients transplanted for CF continues to fall, now accounting for 13% of total adult lung transplants, compared with over 15% five years ago [2, 3]. With constant improvement in knowledge, better management of infective exacerbations, developments in the field of antimicrobials and breakthrough modulator therapy for PwCF, survival has improved in CF patients significantly [4–6]. However, this may have led not only to increasing numbers of PwCF meeting criteria for LTx but unfortunately, also to delayed referrals, referral of sicker patients with comorbidities, and patients with complex colonisations of multi-drug resistant organisms. Despite this, with 9.9 years of median survival and 12.4 years of conditional survival in patients that survive beyond the first year, PwCF demonstrate the best survival compared to any other indication for LTx [2]. Moreover, survival in ISHLT registry (1992 to 2017) stratified in 3 eras show a significant improvement in the survival of PwCF in the recent era when compared with other indications for LTx [2]. This is mainly due to the younger age and good other end-organ function of these patients at the time of transplantation. On the other hand, CF patients when compared to other indications for LTx pose a set of exclusive challenges. Familiarity, experience and expertise of the transplant team to deal with these problems make a significant difference in the outcomes.

## 2. Patient selection

### 2.1 Indications and contraindications of LTx in CF

With a scarcity of donor organs and higher mortality in LTx recipients compared to other organs, health economics would support offering a limited supply of donor organs to recipients expected to benefit the most. However, the onus to identify such recipients falls upon timely referral and listing of the candidates for potential LTx. A clinical window where the patient is symptomatic enough to require LTx but strong enough to survive the operative trauma varies with the individual patient. Generally, when the FEV1 in PwCF drops below 30%, their expected median survival is around 2 years [7]. However, FEV1 is not a reliable indicator of survival as many with CF with longstanding low lung function may survive without transplantation. Currently though, in the absence of a better option, it remains the best available indicator for referral and listing purposes. Inadequacy of clinical parameters to sufficiently

predict survival in CF patients raise a need for mortality prediction models. One of the first such comprehensive models recognised age, respiratory microbiology, height, FEV1, annual number of hospital admissions and courses of home intravenous antibiotics as the most important predictors of 2-year mortality [8]. However, the authors also admit that their model is no better than the widely used FEV1 < 30% predicted. Thus, referral of patients for transplant based either on their model probability of dying within 2 years or on an FEV1 of less than 30% predicted could result in a high rate of premature referral, as a substantial proportion of patients predicted to die within 2 years based on these criteria would survive this period. Therefore, it is wise to take into consideration risk factors associated with early mortality in PwCF when shortlisting them for LTx. One of the biggest CF databases, the UK CF Registry reviewed records from 2005 to 2015 on 6181 individuals, and acknowledged strong associations of *Burkholderia cepacia* infection, CF-related diabetes, and more hospital days on IV antibiotics with decreasing survival [9]. A Canadian CF registry analysis identified older age at diagnosis, diabetes, and deteriorating FEV1 as predictors of reduced survival [10] whilst a recent meta-analysis based upon 11 studies identified *Burkholderia cenocepacia* and ascending chronological year of LTx as predictors of post-LTx mortality [11]. Referring physicians whilst focusing on the FEV1, should also pay special attention to these risk factors for poor survival when considering referral to a transplant centre.

Contraindications of LTx in the CF are similar to other end-stage lung disease causes and are broadly divided into absolute and relative contraindications. A consensus document for the selection of LTx candidates offers a thorough review into the contraindications for LTx (**Table 1**) [12].

### 2.2 Criteria for referral and listing

Early or sometimes premature referral of PwCF to transplant centres offers patients a chance of early transplant assessment to maximise their window of opportunity for donor offers and a LTx. Additionally, early referral has the potential to identify modifiable contraindications to LTx or risk factors of transplant mortality allowing these to be treated and optimised before requiring listing. A delayed referral carries a risk of insufficient time to wait and less number of donor offers to the referred patients. Candidates may miss their window of opportunity and be removed from the waiting list due to clinical deterioration or worse. An ideal time of listing any candidate for LTx is when the benefits from the procedure balance its risk. It is not unusual practice at transplant centres to send patients back to the referring physicians for not meeting the criteria of listing post-assessment but identifying them as future candidates. A 2006 ISHLT update for selection of transplant candidates for the first time separated referral and listing criteria emphasising a timely referral of the end-stage lung disease candidate to transplantation centres [13]. These were revised in a 2014 update as summarised in **Table 2** [14].

### 2.3 Pre-operative work-up

Transplant teams while assessing referred CF patients for LTx should ask two vital questions- (i) Is a transplant required- in other words, is the transplant going to improve survival and quality of life? (ii) Is the patient transplantable? – i.e. is the patient going to survive the transplant?

Transplant evaluation requires a medical assessment, psychological assessment, and in some countries, financial assessment. The medical assessment requires an admission for 2–3 days so that a patient can have multiple investigations and be reviewed by the multi-disciplinary team (MDT) (**Table 3**) [15]. Additional investigations that may be

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| **Absolute contraindications** |
| History of malignancy with less than 5 years of disease free interval |
| Untreatable significant dysfunction of another major organ system |
| Coronary artery disease not amenable to revascularization |
| Acute medical instability (sepsis, myocardial infarction, liver failure) |
| Uncorrectable bleeding diathesis |
| Chronic infection with highly virulent and/or resistant microbes |
| Evidence of active *Mycobacterium tuberculosis* infection |
| Significant chest wall or spinal deformity |
| BMI ≥ 35.0 kg/m$^2$ |
| Current or history of non-adherence to medical therapy |
| Psychologic conditions with inability to cooperate with medical team |
| Absence of adequate or reliable social support system |
| Severely limited functional status with poor rehabilitation potential |
| Substance abuse or dependence |
| **Relative contraindications** |
| Age > 65 years in association with low physiologic reserve |
| BMI 30.0–34.9 kg/m$^2$ |
| Progressive or severe malnutrition |
| Severe, symptomatic osteoporosis |
| Extensive prior chest surgery with lung resection |
| Mechanical ventilation and/or extracorporeal life support |
| Colonisation/infection with highly resistant or virulent organisms |
| Infection with hepatitis B and/or C |
| Infection with HIV |
| Infection with Burkholderia cenocepacia, Burkholderia gladioli |
| Infection with multi-drug–resistant Mycobacterium abscessus |
| Atherosclerotic disease burden |
| Diabetes mellitus, systemic hypertension, epilepsy |
| Central venous obstruction, peptic ulcer disease, gastroesophageal reflux |

**Table 1.**
*Absolute and relative contraindications for LTx in CF.*

required include CT coronary angiogram (CTCA) in PwCF aged over 40 years or right heart catheterisation in severe pulmonary hypertension. All referrals require a dental assessment before listing, but PwCF may require assessment by ENT or gastroenterology doctors in addition. Psychology, palliative care and physiotherapy review during their assessment provides insight on a patient's suitability to undergo transplantation, and social support is also explored during this time. In some countries, financial evaluation is necessary to ensure a potential recipient can afford the immediate transplant care, lifelong aftercare and medications, and management of complications. Following this period of assessment, patients are subsequently discussed at MDT meetings, which include respiratory physicians, transplant surgeons, psychologists, immunologists, radiologists, dietitans and physiotherapists. After discussion, outcomes for each patient

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|---|
| **Timing of referral** |
| FEV1 < 30% pred or falling rapidly despite optimal therapy |
| A 6-minute walk distance <400 m |
| Pulmonary hypertension in absence of hypoxic exacerbation |
| Clinical decline- increasing exacerbations with - |
| (i) Acute resp. failure requiring NIV |
| (ii) Increasing antibiotic resistance and poor clinical recovery from exacerbations |
| (iii) Worsening nutritional status despite supplementation |
| (iv) Pneumothorax |
| (v) Life threatening hemoptysis despite bronchial embolization |
| **Timing of listing** |
| Chronic respiratory failure with hypoxia alone (PaO2 < 8 kPa) |
| Chronic respiratory failure with hypercapnia (PaCO2 > 6.6 kPa) |
| Long-term NIV |
| Pulmonary hypertension |
| Frequent hospitalisation |
| Rapid lung function decline |
| WHO Functional Class IV |

**Table 2.**
*Timing of referral and timing of listing for LTx in CF patients.*

include decision for active listing, further information required, rejection as unsuitable, or deferral as too well.

## 2.4 Waiting list

The time spent by potential recipients on the LTx waiting list depends on various factors including blood group, HLA antibody status and the size of pleural cavities. Whilst on the waiting list, patients are encouraged to exercise regularly, achieve or maintain a healthy BMI, avoid frequent infective exacerbations, and inform any changes in circumstances urgently. Transplant coordinators maintain contact with patients on the waiting list, update records, educate patients and communicate between all members of the transplant team. Traditionally, organ offering systems take into account time spent on the waiting list and the clinical status of the candidates, but influenced by the urgency of transplantation. With this freedom of recipient selection to the transplant centres, fairness in the distribution of the donor organs to the most worthy recipients may be jeopardised. A study looking into 2213 lung-only registrations into the UK Transplant Registry between 2004 and 2014 showed discrepancies between the risk profile and probability of LTx. The chance of LTx after listing differed by the combined effect of disease category and centre, height (taller patients having a greater chance of transplant) and blood group (blood group 'O' having highest waiting mortality) [16].

The ideal recipient for any donor organ is the one with urgent need of transplantation along with the longest expected post-transplant survival. The Lung Allocation Score (LAS) system adopted in the US in 2005 incorporated estimated survival benefit offered by LTx by 1 year after surgery and medical urgency. Since its introduction, the number of deaths on the waiting list in the US has reduced

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| **Blood tests** |
| Full blood count, Coagulation studies, Blood glucose, Blood group |
| Kidney function, Liver function |
| Lipid profile, Thyroid function |
| HLA status, Panel reactive antibody status |
| **Radiology studies** |
| Chest CT, Sinus CT |
| Abdominal ultrasound |
| **Functional studies** |
| Lung function: Spirometry, lung volumes and diffusion |
| Arterial blood gases |
| 6-min walk test |
| Cardiac: ECG, Echocardiogram, right heart catheterisation |
| Bone mineral density |
| **Infection screen** |
| Sputum m/c/s, fungi and mycobacteria |
| Mantoux test |
| Midstream urine |
| Swabs for MRSA |
| Serology for HIV, hepatitis B, hepatitis C |
| Serology for cytomegalovirus, Ebstein-Barr virus, Varicella zoster |
| Serology for Chlamydia pneumoniae |
| **Malignancy screen** |
| Sputum cytology |
| Papanicolau smear |
| Prostate specific antigen |
| Mammography |
| Faecal occult blood screening |
| **Autoimmune screen** |
| ANA, ENA, DNA antibody, Rheumatoid factor, ANCA, Immunoglobulins |
| Creatine kinase |
| Compliance screen Serum cotinine |
| **Consultant referrals** |
| Dental, Ear, nose and throat, Gastroenterology |
| Nutrition |
| Physiotherapy |

**Table 3.**
*Assessment for LTx in CF patients.*

from 500/year to 300/year, the distribution of recipients has changed, and the number of LTx increased despite no substantial increase in organ donors with no decrease in 1-year survival after LTx, even though sicker patients were undergoing transplant [17]. With the introduction of the LAS, the number of LTx for PwCF

increased by 25%, 70% of CF patients were transplanted within 1 year of being listed, and 1-year waiting-list mortality decreased from 15–10% [18]. The LAS was then adopted by Eurotransplant who distribute lungs between donor countries if they cannot be used within the donor's country of origin. After 3 years, the US results were imitated in Germany [19]. However, some reports have shown that the LAS increases the complexity of the post-transplant course and postoperative mortality [20, 21] and in some cases, reduced survival outcomes irrespective of risk profile [22]. Current allocation policy in the US initially utilises donor organ location and age to match with compatible wait-listed patients, followed by the LAS value, ABO blood type, thoracic cavity size and immunological compatibilities to ultimately select a match.

In the UK, between 2004 and 2014, 79.2% of patients with chronic obstructive pulmonary disease (COPD) received a transplant by 3 years of wait on the list versus 61.3% of PwCF and 48.9% of those with pulmonary fibrosis (PF). During the same period, patients with COPD had the lowest mortality on the list. In comparison, PwCF had a 230% higher chance of death on the list without LTx [16]. To optimise this disparity in organ allocation, in May 2017 the Cardiothoracic Advisory Group introduced an urgent and super-urgent lung allocation scheme in which patients at high risk of death without a LTx are prioritised at a national level [23]. In this scheme, patients supported with ECMO (extracorporeal membrane oxygenation) or iLA (interventional lung assist) as a bridge to transplant are prioritised on a national super-urgent waiting list, whilst severely unwell patients particularly in CF patient, worsening hypoxia and hypercapnia, persistently low pH, refractory right heart failure and ongoing massive hemoptysis can be recommended for the national urgent waiting list. Other policies in the UK include small adults (≥16 years of age and ≤ 155 cm of height) receiving offers of lungs from paediatric donors before other adults, (but after paediatric patients,) and priority is given to blood group identical recipients over blood group compatible recipients. In some cases, 'zonal centre' priority is given to patients at a centre if the donor is located within that centre's allocation zone [23]. However, the current system remain inefficient in prioritising patients depending upon the type of lung disease, and building individual risk profiles combining the factors such as urgency, height, and blood group. All current organ allocation systems strive to achieve the best post-transplant survival rates whilst reducing waiting list mortality, but remain far from ideal. Current systems should continue to undergo periodic evaluations, adopt practices from other systems, and remain dynamic to outcome-driven changes. The zonal allocation should depend on a distance rather than arbitrary geographical boundaries.

## 3. Lung transplantation

### 3.1 Donors

Availability of donor organs remains the most important limiting factor for transplantation as lungs, in particular, have the lowest harvest rate. The Eurotransplant registry reports utilisation of lungs from only 698 donors out of 1192 registrants in the year 2019 which is significantly lower compared to abdominal organs [24]. Significant progress has been made in the last decade to improve the donor pool for lungs, but there remains a huge scope for further development. Donation after circulatory death (DCD) is becoming commonplace with a recent review of ISHLT data showing comparable five-year survival in recipients receiving lungs from donors after brain death (DBD) against DCD (63% vs. 61%) [25].

Metanalyses comparing LTx outcomes dependent on the type of donation have shown no difference in survival, primary graft dysfunction (PGD) or acute rejection [26, 27]. Protocol-based management of multiorgan brain dead donors with a focus on lung donation in recent years have significantly improved lung utilisation rates [28]. A ventilation strategy with a low tidal volume and higher PEEP, along with a neutral or negative fluid balance helps protect potential donor lungs [29].

Standard lung donor criteria have been liberalised in the last two decades with an increasing proportion of marginal donor lungs being utilised for LTx with equivalent outcomes. A review of the UNOS database showed reduced 1-year survival with the use of marginal donor lungs, especially in high-risk recipients [30]; however, the survival of these patients on the waiting list without transplantation is questionable. Moreover, it's the high-risk recipients and not marginal donors that are associated with poor outcomes [31]. A lung donor score (LDS) based upon past medical history, smoking history, age, arterial blood gases, chest X-ray, and bronchoscopy findings, that accurately predicts the likelihood of organ acceptance and recipient mortality may facilitate donor risk assessment and patient selection [32]. Ex-vivo lung perfusion (EVLP) is now an established therapy to repair and evaluate marginal lungs for transplantation with comparable post-transplant outcomes [33–35].

To expand the donor pool, more countries are embracing an 'opt-out' system for organ donation. In Europe, the 2018 figures of lung donor utilisation rate were significantly higher in Austria and Belgium (9.8 and 10.8 ppm) where they have opt-out systems for organ donation, compared to Germany and the Netherlands (3.8 and 4.7 ppm) where an opt-in system remains [36]. The waiting list mortality rates in countries with high donation rates are lower compared to those in countries with low donation rates (7% vs. 12% at 1 year), with higher quality donor lungs more often used in these countries with high donation rates, thus offering a chance of better outcomes in recipients [37].

## 3.2 Challenges in LTx for CF

### *3.2.1 Preoperative procedures*

The average annual incidence of pneumothorax in PwCF is 1:167 patients per year and 3.4% of CF patients will experience a pneumothorax during their lifetime [38]. According to current CF Foundation practice guidelines, a chest drain is recommended for large pneumothoraces or small pneumothoraces with clinical instability, whilst surgical pleurodesis is recommended for recurrent, large pneumothoraces [39]. The incidence of CF patients with a history of pleural intervention undergoing LTx is increasing as patients are being offered alternative interventional therapies before resorting to LTx.

The inflammatory/chronic infective component of CF independently contributes to increased pleural adhesions [40]. Dense pleural adhesions encountered during LTx in such patients increases surgical time, bleeding, blood transfusion requirement (that may further increase the chance of primary graft failure (PGD)), renal injury, prolonged respiratory wean and early mortality [41, 42]. Some groups, however, report no difference in operative outcomes despite pleural adhesions in PwCF [40, 43, 44]. It is worth noting that the LAS nor the ISHLT Registry consider previous cardiothoracic procedures as a contraindication to LTx.

In a multicentre study of CT scan scoring in PwCF based on infection/inflammation, air trapping/hypoperfusion, normal/hyperperfusion, and bulla/cysts, infection/inflammation was found to have a significant predictive value for survival [45]. Careful and detailed studies of CTs for pleural thickening, irregularity and

calcification before listing for LTx is recommended to anticipate operative challenges and risk stratification. Avoidance of CPB, starting the procedure on the side of fewer adhesions, minimising blood loss by meticulous adhesiolysis and the presence of an experienced surgeon may prove helpful. PwCF may require lung resection for localised severe bronchiectasis, atelectasis, bronchopleural fistula refractory to medical management and severe hemoptysis refractory to conservative management [46, 47]. This not only causes pleural adhesions, but can also lead to loss of pleural cavity volume. At LTx evaluation, such patients require strategic planning while setting donor size parameters; they may require a donor lung reduction or lobar lung implantation.

*3.2.2 Preop ECMO and mechanical ventilation*

It is not uncommon for PwCF to suffer an infective exacerbation causing acute hypercapnic respiratory failure with worsening respiratory acidosis. Most exacerbations are managed with antibiotics and chest physiotherapy, but some require respiratory support with inhaled oxygen or escalation to non-invasive ventilation (NIV). Patients with deteriorating gas exchange despite NIV either require endotracheal intubation and invasive mechanical ventilation (IMV) or ECMO despite or to minimise IMV. Once an acceptable gas exchange is established with ECMO, sedation wean and extubation or tracheostomy should be performed in these patients to allow for ongoing physiotherapy rehabilitation.

Recent evidence from the UNOS database comprising 14,320 patients in the LAS era showed an association between pre-transplant ECMO and IMV with 30-day mortality as well as prolonged hospital length of stay after LTx [48, 49]. The Extracorporeal Life Support Organisation (ELSO) Registry showed 52% survival in CF patients supported on ECMO [50]. Fuehner et al. demonstrated improved survival in patients bridged to LTx with an "awake ECMO" strategy when compared with those managed with IMV (80% vs. 50% at 6 months), emphasising the potential advantages of minimising time sedated [51]. The key benefits of maintaining patients awake on ECMO is the avoidance of complications associated with sedation, intubation, IMV, and immobilisation. They can undertake active physiotherapy helping to reduce the rate of muscle wasting and preventing pressure sores. Patients are encouraged to eat and drink without enteral feed if possible. Meeting family and social media helps to maintain a positive mood, and suboptimal therapy or complications can be detected at an earlier stage as patients can identify and communicate symptoms of dizziness, breathlessness, and pain [52].

### 3.3 Procedure of LTx

Despite early success and advantages of heart-lung transplantation for CF (fewer anastomoses, shorter ischaemic times and re-utilisation of recipient's heart in a "domino" transplant), it has been superseded by LTx due to donor organ shortage and equivalent outcomes [53]. Bilateral sequential LTx in which unilateral pneumonectomy and donor lung implantation are performed in sequence is the standard operation for a suppurative disease like CF. However, single-LTx after synchronous or metachronous contralateral pneumonectomy for PwCF resulting in an asymmetric chest and lung volume mismatch may be an acceptable functional therapeutic option [54, 55].

The CF patient population consists of a large proportion of children and small adults that are not suitable recipients for most adult sized donors leading to an increase in the waiting list mortality. For a marginal size mismatch, peripheral lung resection, also known as 'lung shaving' may suffice, however, donor lung lobectomy

to utilise only the upper or lower (preferred option) lobe dependent on the recipient pleural cavity size may be required [56, 57]. Bi-partitioning lobar LTx is a bilateral lobar transplant from a single donor lung. This can be performed to maximise the donor pool, but is not a popular procedure due to technical challenges [58]. Living-donor lobar LTx (LDLLT) is lifesaving in countries with low cadaveric donation and for patients deemed unable to await a cadaveric LTx [59]. Two lobes obtained from live donors can adequately support an adult CF patient and the morbidity from lobectomy to the healthy donor is minimal. A study where 84% of the cohort were CF patients undergoing LDLLT showed a survival of 70% and 45% at 1 and 5 years, which is comparable with double-lung cadaveric transplantation according to the ISHLT Registry (74% and 49.5% at 1 and 5 years) in in the same year [60].

### 3.4 Advances in LTx surgery

#### *3.4.1 Minimally invasive LTx*

For double LTx in CF, the clamshell is a conventional approach that offers a direct vision to the heart and lung hila, but can cause sternal dehiscence, malalignment, wound dehiscence and rarely mediastinitis. These complications are thought to be under-reported, but cause significant morbidity through readmissions, multiple surgical debridements and prolonged wound care. Infection can be difficult to treat in the presence of steroid-induced osteoporosis, breathing-induced mobility in healing sternal edges, and immunosuppression. Sternal sparing bilateral thoracotomy approach may be less painful and may support early extubation, ambulation, and rehabilitation [61]. This approach spares the internal mammary arteries, causing less blood loss, and is superior cosmetically to the clamshell incision. A requirement of long instruments and telescopic surgical skills for this approach is a myth. Utilisation of a modified rib spreader, with movable and adjustable blades provides optimum exposure without injuring the ribs. For emergency conversion to CPB, apart from peripheral access via the groin, one can cannulate via the thoracotomy.

#### *3.4.2 Role of mechanical circulatory support in LTx surgery*

Double LTx is conventionally performed with the aid of cardio-pulmonary bypass. As bilateral sequential LTx became commonplace, the use of CPB during the procedure declined. A comparative study of LTx in CF shows that the implantation of both lungs on CPB after bilateral pneumonectomy and airway decontamination does offer a protective effect against early graft infection [62]. CBP provides complete respiratory support and haemodynamic stability, ease of hilar dissection and retraction of the heart during the LTx, but can induce an inflammatory response, bleeding, (and thus increased requirement of blood transfusions), and a higher incidence of PGD [63]. Significantly lower survival was observed in CF patients undergoing LTx with the utilisation of extracorporeal circulation [64]. Off-pump surgery may avoid complications caused by circulatory support but is susceptible to periods of hypotension, hypothermia, and hypoxia. It also exposes the new lung to the entire cardiac output potentially causing acute lung injury and PGD.

Off-pump LTx may require emergency conversion to CPB in case of inability to tolerate single lung ventilation, hemodynamic instability, or uncontrolled bleeding. Off-pump LTx requiring emergent conversion to CPB is by default a part of the on-pump group in several reports comparing on-pump and off-pump procedures, which has found worse outcomes in the on-pump group [65, 66]. In the quest of a fair comparison, a further study segregated cases with unplanned CPB conversion and found that despite this segregation, patients with comparable preoperative demographic

and risk profiles demonstrated better early postoperative outcomes including early survival with an off-pump strategy for LTx in comparison to an on-pump strategy. While a considerable proportion of high-risk patients require intraoperative conversion from off-pump to CPB with suboptimal outcomes, there is no significant benefit to employing an elective on-pump strategy in this high-risk group [67]. Although elective use of CPB for LTx has decreased in recent years, mechanical circulatory support of some form is still necessary during LTx in the presence of pulmonary hypertension, suboptimal cardiac function, severe respiratory disease, and marginal donor organs with an insufficient gas exchange when performing one-lung ventilation. Instead of CPB, ECMO that can potentially be continued post-operatively until the donor organs recover and pulmonary pressures alleviate is increasingly being utilised. ECMO offers cardiopulmonary support without cardiotomy suction, venous reservoir, a large amount of prime, and may avoid some complications associated with CPB. A meta-analysis of 7 studies comprising 785 patients comparing CPB and ECMO in LTx showed a lower rate of primary graft dysfunction, bleeding, renal failure requiring dialysis, tracheostomy, intraoperative transfusions, intubation time, and hospital stay along with a trend towards lower mortality in the ECMO group [68]. Elective use of mechanical circulatory support in LTx for CF is now limited to severe secondary pulmonary hypertension or if additional cardiac surgery is required, such as atrial septal defect closure. Optimisation with Milrinone and nitric oxide before a trial of pulmonary artery clamping can be helpful to assess if mechanical support may be required. If there is hemodynamic instability and inadequate gas exchange on single lung ventilation, the operation should continue under ECMO support, whilst emergency CPB can be ustilised in case of catastrophic bleeding, irreversible arrhythmia or hemodynamic instability.

#### *3.4.3 Re-transplantation*

CF patients often become candidates for re-transplantation due to their young age at the time of their primary transplant. PwCF have overall good post-transplant survival but also suffer a higher incidence of bronchiolitis obliterans syndrome (BOS). BOS, primary graft failure (PGD) and irreversible airway complications (stenosis and dehiscence) are the main causes for lung re-transplantation. Pseudomonal airway colonisation before and after LTx is thought to be associated with the increased prevalence of BOS in CF patients [69]. CF recipients are at higher risk of acute cellular rejection and subsequent BOS due to the enhanced immune activation associated with CF, their younger age and higher prevalence of donor specific antibodies [70, 71]. Scarcity of donor organs and suboptimal outcomes have always raised doubts about the validity and ethics of re-transplantation, especially as historically, the survival post-re-transplantation has remained inferior compared to the primary transplantation. Interestingly though, rates of BOS has shown an improved trend with 1-year survival increasing from 47% in the 1990s to 72–78% in the last 15 years [73–75]. Re-transplantation in non-ambulatory, ventilated patients, with PGD, anastomotic dehiscence, or less than a year since primary transplantation is associated with higher mortality [72–75]. Careful recipient selection with preoperative optimization in terms of nutrition and functional status, along with end-organ function are vital for successful re-transplantation.

## 4. Complications of LTx in CF

PwCF continue to demonstrate the best survival compared to other indications for LTx [76, 77], but suffer the same complications as those without CF to varying

extents. Within the first month, primary graft dysfunction, acute infections, and technical complications dominate the cause for admissions, transitioning to also include rejection in the first year. Rejection and infection remain complicating factors throughout a recipient's life, with malignancy an increasing risk the longer a recipient remains on immunosuppression [77, 78].

### 4.1 PGD

Primary graft dysfunction (PGD) is the main cause of death within the first 30 days post-operatively [78], and is a form of acute lung injury that involves a wide spectrum of signs and symptoms within the first 72 hours of transplantation. For this reason, it is also known as the "re-implantation response". PGD is the consequence of an inflammatory response triggered by injury to the donor, graft or recipient, ischaemia, and reperfusion, and can cause a decrease in oxygenation with minimal pulmonary infiltrates caused by oedema, through to complete graft failure and death or re-transplantation. PGD is caused by the activation of pulmonary macrophages and circulating leukocytes and is divided into two phases – a first acute phase of lung schaemia and reperfusion injury, which drives the second phase mediated by massive neutrophil recruitment which amplifies the initial innate immune reaction.

A number of risk factors for development of PGD have been identified; in general, donor factors tend to impact the initial 24 hours post-transplantation, whilst the recipient factors affect later outcomes. Donor-related risk factors include sex, age, smoking history, ischaemic time, and brain-death-associated lung injury [79, 80]. Given the underlying pathophysiology of PGD, the approach to management is based on the treatment of ARDS (acute respiratory distress syndrome) using protective IMV and maintaining a negative fluid balance. However, this treatment plan is complicated by patients who may not tolerate permissive hypercapnia cardiologically, and fragile renal function due to multiple insults in the operative and immediate post-operative period.

It has been shown that lung recipients who develop PGD have a marked graft and systemic inflammatory response, and that the timing and grade of PGD severity has implications to the risk of developing BOS (bronchiolitis obliterans) later [81, 82].

### 4.2 Infections

Post-transplant infections remain a significant source of morbidity and mortality in all recipients, but this is complicated by the nature of the multi-resistant organisms found in CF recipients due to repeated antibiotic courses. It has long been accepted that PwCF are chronically colonised with bacteria, and so finding positive microbiology in the sputum of transplanted PwCF does not necessitate an acute infection, but equally, transplanting the lungs does not eradicate individuals with CF of the bacteria which remain colonised in the upper airways and the sinuses. PwCF colonised with *Mycobacterium abscessus* or *Bulkholderia cenocepacia* cannot be transplanted in most centres due to the high morbidity and mortality rates associated with these conditions post-transplantation. Though there have been some success in transplanting PwCF who have negative sputum for *M. abscessus* pre-transplantation but remain on treatment [83–85].

It is just as important to consider the donor's microbiological profile. All donors are screened for obvious reasons for HIV, hepatitis B and hepatitis C, but where donors have died from undiagnosed infections, the risk of transmitting a potentially lethal infection into a recipient has to be considered. In addition, the longer

a potential donor is ventilated, the more likely they are to become colonised with antibiotic-resistant flora, complicating a future transplant. BAL before harvesting or implantation is useful to culture and therefore guide antibiotic management in the peri-operative and immediate post-operative period.

Like any major surgery, surgical site infection can also occur. Good peri-operative lavages of the donor lungs and the recipient's pleural cavity is important to reduce the presence of infected material. It is often difficult for antibiotics to penetrate the pleural cavity so although infections at a wound site are unusual, once present, they can be difficult to manage and treat. Again, PwCF are at higher risk of infections at anastomotic and surgical sites by the nature of the underlying disease. The antibiotics selected peri-operatively and post-operatively are guided by the patient's response to antibiotic combinations pre-operatively, as well as microbiological sensitivities. Just like other intensive-care patients, post-transplant patients are at high risk of ventilator-associated pneumonia (VAP), and so unless there are contraindications, it is important to work towards extubating the patient as expediently as possible.

CMV (cytomegalovirus) disease used to be a significant concern post-transplant, but the routine use of prophylactic and treatment valgangiclovir combined with surveillance management has significantly reduced the risk of infection or reactivation [86]. A recent study looking at the incidence of CMV infection in heart transplant recipients has estimated the rate of early-onset (<100 days post-transplant) CMV disease at only 2%, compared with late-onset (>100 days post-transplant) at 7.5%, and this is largely thought to be due to the introduction of valganciclovir [87]. EBV (Epstein–Barr virus) mismatches where the donor is positive and the recipient negative, are rare as >95% of the population seroconvert by the time they are 20 years of age. Most recipients undergo a B-cell proliferation 1–3 months post-transplant, but occasionally this can proceed to a post-transplant lymphoproliferative disease (PTLD). Monitoring of EBV levels is generally used as a marker of over-immunosuppression rather than a way of looking for malignant disease. Similarly, with the widespread use of co-trimoxazole as first-line prophylaxis, PCP (pneumocystis pneumonia) – also known as PJP (*pneumocystis jiroveci pneumonia*) – is an unusual finding, with rates in solid organ transplant recipients reduced from 5 to 15% to 0.3–2.6% [88]. Other respiratory viruses that can have significant impact to a transplant recipient includes respiratory syncytial virus (RSV), metapneumovirus, influenza/parainfluenza, adenoviruses and rhinovirus. Any of these can cause a viral pneumonitis, which can in turn inflict permanent damage to the transplanted lungs, either through the inflammatory process of an infection, or by triggering acute rejection or chronic allograft dysfunction (CLAD) [89]. Most of these infections have no direct treatment, and so management remains supportive with the addition of IV methylprednisolone and/or IV immunoglobulin (IVIG) in an effort to prevent rejection which can be triggered by these viral infections [89].

Many PwCF are often sensitised to *Aspergillus fumigatus* and will often be on longterm oral antifungals that will need to continue following transplantation. For all causes, invasive aspergillosis is the most common cause of all invasive fungal infections in lung transplant recipients [90], but it can also be asymptomatic. Often however, it will lead to a more pathogenic process, including causing anastomotic dehiscence and lung function decline without obvious radiographic changes [91]. This process is still not fully understood, which often results in trials of treatment to find the most effective. *A. fumigatus* accounts for 44% of fungal infections in the post-lung transplant population, but other common fungal infections post-transplant include *Candida* (23%), *Scedosporium* (20%), *Mucorales* (3%) and *Cryptococcus* (2%) [92]. Throughout a recipient's lifetime, it is often difficult to tell the difference between rejection and infection as no reliable markers exist. Recipients are subjected to frequent invasive investigations (usually bronchoscopy)

especially in the early post-transplant period, requiring washings and biopsies to differentiate. Patients are encouraged to attend their transplant centres as their local referring centre which usually treat patients as having infections rather than consider or have the means to investigate for a diagnosis of rejection. This is especially true for PwCF as they are likely to remain positive for their primary pre-transplant pathogenic bacteria. It is important to keep in mind that they are also susceptible to the same atypical infections as all other lung transplant recipients are, and that even if a diagnosis of infection is correct, it may not be caused by the same causative organisms as per prior to transplantation.

Part of keeping transplant recipients well includes maintaining appropriate prophylactic antibiotic cover. In CF recipients, this often means continuing the oral anti-fungals or nebulised antibiotics they were on pre-transplant for a number of months at least. If these recipients remains well with no positive microbiology, an informed decision to reduce the prophylaxis burden could be considered. All recipients are advised to maintain annual vaccines such as the flu vaccine, but other vaccines should be discussed with transplant centres as not all vaccines are appropriate in the immunosuppressed population.

### 4.3 Rejection

The first 2 months post-transplant are high risk for acute rejection, as recipient lymphocytes encounter donor antibodies for the first time. However, the risk of death is low with acute cellular rejection (ACR), and this decreases even further with time [93]. Longer term, the risk is of bronchiolitis obliterans syndrome (for which ACR is a risk factor) and CLAD. Unlike most other solid organ transplants (SOT), lung transplantation has always required a fine balance between adequate immunosuppression and the risk of infection. Many patients end up with varying individualised immunosuppression based on the number of rejection episodes against the rate of infections each person has 28% of surviving lung transplant recipients between 2004 and 2015 required treatment for acute rejection in the first year post-discharge [3]. Most recipients will require treatment for acute rejection in the first year post-transplant, usually in the first 6 months [94]. Treatment is usually a short course of high dose IV methylprednisolone (IVMP) for 3–5 days, followed by a tapering course over 2–3 weeks. If a patient suffers from recurrent bouts of acute rejection and treatment adherence is confirmed, then immunosuppression may need to be increased if tolerated renally. Where acute cellular rejection is refractory to standard treatment, other modalities of treatment are available. RATG has variable success but is still used. Total lymphoid irradiation (TLI) and extracorporeal photophoresis are both used with a degree of success in slowing the rate of lung function decline, sometimes halting it altogether [95, 96].

Chronic lung allograft dysfunction (CLAD) remains a major barrier to long-term survival post lung transplantation. Until recently, CLAD and bronchiolitis obliterans syndrome (BOS) were used interchangeably. However, the heterogeneity of the clinical course of CLAD along with highly variable responses to treatment has caused clinicians to review radiology and histology and suggest two distinct phenotypes: BOS and restrictive allograft syndrome (RAS) (also known as restrictive CLAD (rCLAD)). BOS is characterised by an obstructive picture on pulmonary function tests, air trapping on CT imaging, and obliterative bronchiolitis (OB) on histology [97]. RAS is characterised by restrictive results on pulmonary function tests, pleuro-parenchymal infiltrates on CT and fibro-elastosis on biopsies [98]. It is important to differentiate between the two as patients with RAS have an average expected life expectancy of 6–18 months following diagnosis, compared to 3–5 years after diagnosis of BOS [97].

### 4.4 Malignancy

With improved survival post-transplant, long term complications are increasingly common. Lung transplantation requires higher amounts of immunosuppression compared with most other solid organ transplants, which increases the risk of developing cancer due to impaired anti-tumour immune surveillance and anti-viral activity. Malignancies occur in 18% of patients reaching 5 years of survival, and 28.7% of patients reaching 10 years of survival [99]. Malignancies transmitted from the donor are rare due to the surveillance undertaken at the time of donation [100].

PTLD is diagnosed when EBV levels start to rise in association with an abnormal white cell count, and is more common in lung transplant recipients than most other SOT recipients. It occurs in 2–9% of lung transplant recipients [101, 102]. Early cases (within 1 year of transplantation) typically involve the lungs and occur in recipients who have not previously been exposed to the virus, whereas cases presenting more than 1 year post-transplantation are more likely to involve the gastrointestinal (GI) tract [101]. Radiologically, lymphadenopathy and pulmonary nodules in the peripheral and basal zones are seen on CT [103]. Post-transplant immunosuppression impairs T-cell-specific immunity against EBV but EBV-negative PTLD has also been recognised. Early-onset PTLD is more likely to respond to a reduction in immunosuppression than late-onset as the pathogenesis of the latter is less well understood, but this in turn increases the risk of rejection and graft failure [104]. As a result, prognosis with late-onset PTLD is worse [102, 105]. If reduction in treatment is not the solution, the next option would be rituximab, which induces cell death of B-cells via CD20 which is on the surface of these cells.

Non-melanoma skin cancers are the most common skin cancer for SOT recipients and this is also true in LTx [106, 107]. All lung transplant recipients are advised to monitor their skin for any suspicious changes, and regular review by their GP or a dermatologist is often recommended. They are also cautioned about time spent in the sun and advised to use high factor sun cream liberally. Squamous cell carcinomas (SCCs) are 100–200 times more likely to occur post-lung transplant compared to the general population [107], and they are usually more aggressive with high rates of recurrence [102]. All other forms of skin cancer are more common than the general population but not to the same extent. The increased risk of non-melanoma cancer in all SOT recipients is primarily due to immunosuppression which affects the usual cellular pathways that prevent cancerous growths. With LTx recipients receiving the highest levels of immunosuppression, it is unsurprising that this group of patients have the highest rates of skin cancer. There is also increasing evidence that voriconazole increases the risk of SCC [108] and so it is advised to reduce the length of treatment time if possible and otherwise switch to an alternative anti-fungal that appears to have less of an association with cancer.

Treatment is identical to all other skin cancer treatments, aiming for local excision with complete clearance, but if possible, rates of immunosuppression should be reduced to reduce the risk of recurrence or further skin cancers. Radiotherapy is an alternative option for those who are high risk for surgery or whose cancers have progressed to being inoperable [109]. Monoclonal antibodies have had increasing success in the general population, however, these have not been tried to a great extent in post-transplant recipients due to concerns over their interaction with immunosuppression and risk of graft rejection.

Lung transplant recipients appear to have up to a 5-fold increased risk of lung cancer compared to the general population [110], but the risk is primarily related to pre-transplant risk factors and so there is a higher incidence in those transplanted for COPD or ILD. For PwCF, the risk of developing lung cancer is generally donor-related risk factors or due to immunosuppression as described earlier. When lung

cancer does develop, treatment remains challenging as no treatment has been well-studied alongside immunosuppression, and outcomes are often poor.

Although all SOT recipients are at increased risk of developing colorectal cancer, LTx recipients who have CF have a significantly higher incidence, even within the transplant population [111]. This is presumed to be due to the inherent risk of GI malignancy in all PwCF compounded with the increased incidence due to immunosuppression. The US-based CF Foundation have recently published Consensus guidelines for colorectal cancer screening in PwCF which should be followed post-transplant also [112]. Further information on colorectal cancer in CF can be found in the chapter entitled "Digestive System".

## 5. Conclusions

Although lung transplantation in PwCF has achieved results once thought impossible, there remains substantial opportunity for progress. Avenues for these opportunities include better donor management and organ preservation, improved donor allocation systems to offer organs to those most in need who will also benefit most, optimization of recipients in terms of physiology, GERD management and CFRDM, and prevention of PGD, rejection, and infections. Preoperative pleurodesis and lung resections are not contraindications to lung transplantation, however, strategic planning with CT imaging and availability of experienced team members may reduce complications. While preoperative mechanical ventilation is potentially detrimental, patients should be bridged to lung transplantation with ECMO support, aiming to wake them as soon as is feasible. Bilateral thoracotomy approach is superior to the conventional clamshell cosmetically as well as in regards to wound complications. Elective use of mechanical circulatory support in LTx for CF is now limited to severe secondary pulmonary hypertension or additional cardiac surgery, and in the case of hemodynamic instability or inadequate gas exchange on single lung ventilation, the operation should be performed under ECMO support.

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