Lung transplantation

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Code: 251 **Updated:** December 01, 2024

Background

Lung transplantation (LTx) is the ultimate treatment option for patients with end-stage lung disease. Cystic Fibrosis patients represent more than one-fifth of the lung graft recipient population and they have the highest rates of post-LTx survival (Roux A, 2019) . Data from the USA Registry (Hayes D Jr, 2016) had showed that children (<18 years old patients) are at higher risk of post-transplant mortality than adults, but a more recent survey(Waseda R, 2018) about all patients younger than age 18 years, who underwent primary lung transplantation at Medical University of Vienna between 1990 and 2015, has showed that outcomes for pediatric lung transplantation have improved over the past 25 years and have become comparable to those for adult transplantation A recent study has been focused to determine which measures of pretransplant physical condition correlate with positive post-transplant outcomes in children undergoing lung transplant. (Freiberger D, 2021)

Reported percentages of CF patients survival, on the whole, are 90%, 86%, 79%, 73%, 60% e 40% at 1, 3, 5, 10, 15 e 20 years respectively after transplantation (Fakhro M, 2016) The results may become better and better overtime (Roux A, 2019), even if a more recent retrospettive analysis by Toronto lung transplant Center (YeungJC, 2020) the 1-, 5-, and 10-year probabilities of survival in adults who were BCC-negative were 94%, 70%, and 53%, respectively.

LTx guidelines, for patients affected by all the end-stage lung diseases, have been published by the International Society for Heart and Lung Transplantation (Orens JB, 2006), updated later as Specific European Lung Transplantation Guideliness in Cystic Fibrosis (Hirche TO, 2014) and more recently revised (Ramos KJ, 2019). A recent CF Foundation consensus has been published, about 32 recomandation statements for the care of CF lung recipients (Shah P, 2021).

Listing for lung transplantation should be considered at a time when survival from respiratory related complications from CF is considered to be less than survival after lung transplantation. Historically, the forced expiratory volume in 1 second (FEV1) has been the most often used functional variable to predict prognosis, with early reports of a FEV1 less than 30% predicted being associated with a 2-year mortality of 50%. Other variables associated with a high risk of death from CF are hypoxia, hypercapnia, pulmonary hypertension, reduced 6-minute walk distance and female sex. From these variables, predictive models of survival in patients with CF have been (Nkam, L, 2017) developed and, recently, revised (Hajizadeh N, 2021), also for pediatric CF patients(Solomon M, 2021).

Recently, CF center directors in the US were surveyed about LTx. Questions addressed transplant referral indications, contraindications, testing, and the impact of ETI on referral timing. Thematic analysis was used to assess responses to open-ended questions. Respondents identified several referral indications, including rapid decline in FEV_1 (93%), recurrent hemoptysis (80%), hypoxemia (79%), and pulmonary hypertension (75%). Respondents were more likely to find early LTx discussions useful for patients not on modulators versus on modulators (87% vs. 63%, $p < .005$). Most respondents (66%) reported delaying LTx referral for some patients with FEV_1 30%-40% who met criteria, while 26% had delayed referral for patients with FEV_1 < 30%. Uncertainty regarding optimal LTx referral timing for patients on ETI was a prominent theme of the qualitative analysis. While physician knowledge about LTx referral indications appears improved since the CF referral guidelines were published, uncertainty about referral timing is pervasive, and the guidelines will need to be updated as more data become available about the long-term effectiveness of ETI in advanced lung disease (Burdis N, 2024).

The absolute and relative contro-indications for lung transplantation are constantly in flux as surgical techniques and management of complications has improved over the past decade (Morrell MR, 2016). Recently, it has been affirmed (Koutsokera A, 2019) that, while B. cepacia complex remains associated with a higher post-LTx mortality, pulmonary hypertension, low BMI, CFRD and female gender have resulted not associated with post-LTx higher mortality.

Because, up to now, a considerable number of patients die on the waiting list before suitable organs become available, donor organ allocation has been realized and discussed in some countries to optimize donor use (Gottlieb J, 2014) (Vock DM, 2017), (Brahmbhatt JM, 2022), (Ramos KJ, 2022)

To face the problem of the relative unavailability of donors the lobar lung transplantation (Barr ML, 2005) above all for small-size recipients, has been performed and new procedures to increase the number of possible donors have been investigated (Valenza F, 2016).

Current methods (Gu C, 2020) for improving the situation of shortage of lung transplant donors include the use of donation after cardiac death (DCD) donors, smoker donors, and Ex Vivo Lung Perfusion (EVLP)

Patients with respiratory failure requiring mechanical support with ventilation and/or extracorporeal membrane oxygenation can mantain outcomes comparable with the other patients with CF (Morrell MR, 2016). (Roux A, 2019)

Complications from lung transplant remain the second most common cause of death in cystic fibrosis (Li SS, 2018).

Most early deaths (within 30 days) following lung transplantation for CF are caused by infection (Lobo LJ,2014) primary graft dysfunction, cardiovascular failure, and acute graft rejection. Recently a review (Vazirani J, 2021) has summarized current and novel therapies to assist with the management of multiresistant bacterial, mycobacterial, viral and fungal infections which threaten CF patients after lung transplantation

After the first month, bronchiolitis obliterans syndrome (BOS), caused by a complex immuno-pathogenetic process and characterized by progressive airflow obstruction, is the major cause of rejection and death. It was stressed that close attention to gastroesophageal reflux disease (Mendez BM, 2012) and to persistent Pseudomonas aeruginosa (Pa) colonization of paranasal sinuses (Vital D, 2012) is needed to prevent BOS in CF transplanted patients. Post-transplant lymphoproliferative disease (PTLD) is another important late cause of morbidity and mortality following lung transplantation (Lowery EM, 2017).

Up to now (Burcharm P, 2017) there is limited evidence for the optimal post-LTx immunosuppression regimen in patients with CF, particularly in children (Sweet SC, 2017).

Recently, CFTR modulators therapy in CF lung transplanted patients has been debated (Tissot A,2022) (Ramos KJ, 2022) and it has been affirmed that further studies are needed to determine the new therapy risk and benefit. Registry-based data could help to define this issue. A study of the US Cystic Fibrosis Foundation Patient Registry (CFFPR) described the effect on lung transplentation referral in subjects with CF who initiated ELX/TEZ/IVA between October 2019 and December 2020. The annualized rates of lung transplantation (0.16% [95% CI: 0.12, 0.22]) was considerably lower than reported in 2019 (1.08%) (Bower JK, 2023).

Unfortunately, CFTR modulator therapy is not effective in all patients, and efficacy varies among patients; it is not a cure, and CF remains a progressive disease that leads predominantly to respiratory failure. Lung transplantation remains a lifesaving treatment for this disease. A recent review assesses the current knowledge of lung transplantation in PwCF, the challenges associated with its implementation, and the ongoing changes to the field as we enter a new era in the care of PwCF (Huang W, 2023).

Issues

- Clinical and microbiological criteria to include patients in the waiting list.
- Optimal surgical techniques, organ preservation and intensive care management.
- Optimal post-transplant management of infections, mainly airway infections.
- Optimal immunosuppressive drug therapy.
- CFTR modulators therapy impact

What is known

One recent Cochrane Review (Saldanha IJ, 2018) on immusuppressive drug therapy for preventing rejection following lung tranplantation in CF didn't include any study due to the lack of information specific to people with CF. No RCT have been found restricted to CF patients. Three studies, in which tacrolimus and cyclosporine have been compared in all lung transplant recipients, reported no significant difference in mortality and risk of acute rejection; tacrolimus use was associated with lower risk of BOS and arterial hypertension and higher risk of diabetes mellitus

One RCT, published in 2000, (Aris RM, 2000), demonstrated pamidronate efficacy in improving post-transplant osteoporosis.

One study , published in 2001, (Doyle RL, 2001) studied the safety and pharmacokinetics of two different dosages of a new macrolide (RAD), used as immunosuppressive agent in CF patients compared to no-CF patients. The results showed no difference between CF and no-CF people.

One study, published in 2008 (Vilkinson OM, 2008) , showed that the use of telemedicine may enhance the support that a specialist unit can provide for the patients and their families in the pre-transplantation follow-up.

One study , published in 2009 (Vandemheen KL,2009), showed that the use of an evidence-based decision aid, specifically developed for patients with cystic fibrosis referred for lung transplantation, may improve patient knowledge and satisfaction.

One study, published in 2013 (Lobo LJ, 2013) showed that a good survival after lung transplantation is possible also in CF patients with M. abscessus in airways.

One study (Zeriouh M, 2018) showed that a taurolidine 2% bronchial lavage might be associated with a reduced proportion of CF patients colonized with multiresistant pathogens, particularly with P. aeruginosa.

Unresolved questions

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- Optimal surgical techniques, organ preservation and intensive care management.
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Some studies are ongoing

Prognostic Value of Functional Exercise Test (EFX) in Cystic Fibrosis (NCT02994017). So far, no result or publication is available.

To test whether a research website improves patient preparedness for discussions about lung transplant. (NCT05135156). This trial is completed and some preliminary results are available (https://www.clinicaltrials.gov/study/NCT05135156?cond=Cystic%20Fibrosis&intr=Lung%20transp

Further research on this issue is ongoing: Lung Transplant READY CF 2: A Multi-site RCT; ClinicalTrials.gov ID NCT06030206

To implement a clinical tool utilizing predictors of mortality for patients with Cystic Fibrosis (CF) on the waiting list to identify candidates that should present for urgent medical care (NCT04687475). The trial should be completed on 2024, 30 June.

Keywords

Immunosuppressive Agents; Transplantation;