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Lung Transplant for Cystic Fibrosis

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Abstract This article reviews lung transplants for cystic fibrosis (CF) patients. Advances in medical therapy have resulted in increased survival for CF patients. Respiratory failure continues to be the leading cause of mortality. CF is a complex disease and a challenge for both CF and transplant physicians. This review covers the recent literature related to aspects of pre-lung-transplant mechanical ventilation and pre/post-transplant infection management. We also review post-operative management of the broad range of systemic complications related to cystic fibrosis, including diabetes, malnutrition, CF-liver disease, and malignancy. Improvements to surgical technique, organ procurement and preservation, and post-operative management in the intensive care unit could improve overall survival.

Keywords Lung transplant · Cystic fibrosis · Respiratory failure · Lung allocation score

Introduction

In 1983, the University of Pittsburgh performed the first lung transplant on a patient with end-stage lung disease from cystic fibrosis (CF). Since the mid-1980s lung transplantation has steadily increased, with approximately 3,500 transplants performed annually worldwide. CF is currently the third most common indication for bilateral lung transplant, with 5,688 performed between January 1995 and July 2011 [1•]. The International Society for Heart and Lung Transplantation (ISHLT) registry reports survival figures of 79 % at one year, 64 % at three years, 53 % at five years, and 30 % at 10 years. CF patients consistently have the highest reported long-term survival after lung transplant (Fig. 1).

Cystic fibrosis is an autosomal recessive genetic disorder caused by a mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene, which encodes and produces a defective chloride channel resulting in multi-organ disease [2]. With advances in medical therapy, the median predicted survival age for people with CF has risen steadily over the last 25 years. In 2011, the median survival age was 36.8 years [3]. Despite therapeutic advances respiratory failure accounts for most morbidity and mortality, and lung transplant is the only treatment option to improve survival. Although, among all lung diseases requiring transplants, median survival is longest for CF patients, post-transplant complications are the second most common cause of mortality [3].

Referral and Evaluation

CF is a complex disease which causes multiple comorbidity, including chronic respiratory failure from infections, liver dysfunction, pancreatic insufficiency resulting in diabetes, chronic sinusitis, and chronic malnourishment. Assessing the appropriate timing for lung transplant referral and for the transplant itself is a continual challenge for both CF and transplant physicians. As well as medical comorbidity, psychosocial difficulties greatly affect overall outcomes in the pre and post-transplant periods.

The current international guideline recommendations for referral are a forced expiratory volume in one second (FEV_1) less than 30 % of the predicted value or rapidly progressive respiratory deterioration (e.g. increasing frequency of exacerbation requiring antibiotic therapy, recurrent hemoptysis not controlled by embolization, refractory and/or recurrent pneumothorax) with an FEV_1 greater than

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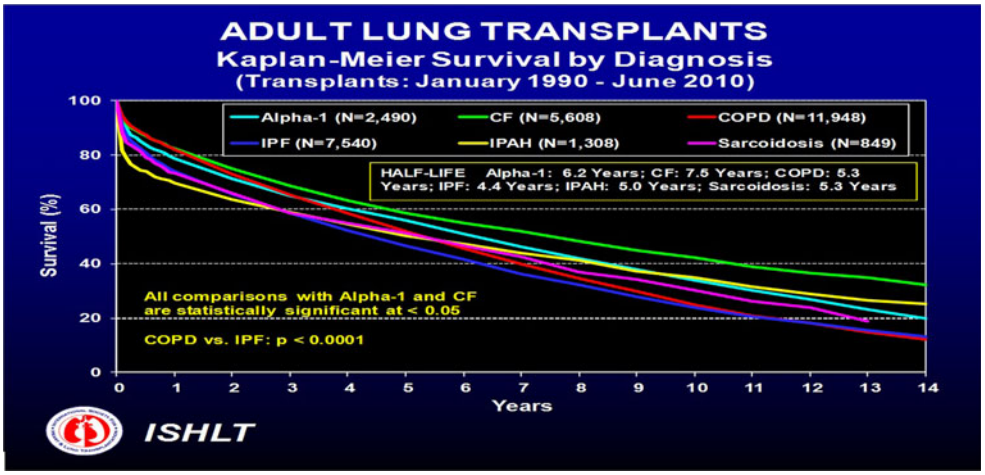

Fig. 1 Adult lung transplants (J Heart Lung Transplant. 2012 Oct; 31(10):1045–1095)

30 % of the predicted value (Table 1). Absolute contraindications are criteria assessed as having a high probability of contributing to increased risk of morbidity and mortality post-lung transplant (Table 2). Relative contraindications include osteoporosis, malnutrition, severely limited functional status with poor rehabilitation potential, poorly managed medical problems (e.g. gastroesophageal reflux and diabetes), mechanical ventilation, and psychosocial dysfunction (e.g. medical non-compliance) [4]. To maintain eligibility as an active lung-transplant candidate, patients must demonstrate ongoing adequate management of any preoperative psychosocial difficulties. Guideline recommendations for transplant are oxygen-dependent respiratory failure, hypercapnia, and pulmonary hypertension [4].

Kerem et al. showed, via regression analysis, by use of models with single covariates, that FVC below 40 % predicted value, FEV1 below 30 % predicted value, PaO_2 less than 55 mm Hg, $PaCO_2$ greater than 50 mm Hg, and weight–height percentage (weight as a percentage of the ideal weight for height and sex), were stronger predictors of greater than 50 % mortality within two years of transplant than any other factor except age and gender. However, use of the same covariates in multiple-variable models found the strongest predictors of increased mortality to be age (less than 18 years of age), sex (female), and FEV1; this three-variable model was most useful for predicting high mortality [5]. Mayer-Hamblett et al. showed, by use of univariate logistic regression, that significant predictors of two-year mortality included number of hospitalizations for acute exacerbation, number of home intravenous antibiotics courses, respiratory colonization with *B. cepacia* and *P. aeruginosa*, weight and height percentile, FEV_1 % predicted value, and age. Colonization with both *B. cepacia* and *P. aeruginosa* was associated with the greatest probability of dying within two years (odds ratio (OR): 4.1; 95 % CI: 2.4, 6.9) in comparison with CF patients not colonized with either organism [6].

Although there is evidence of poorer transplant outcomes [4] for patients with respiratory failure who use mechanical ventilation, many centers have reported successful transplant outcomes for these patients. Bartz et al. compared outcomes for eight CF patients who underwent mechanical ventilation for 62±20 days (range 3–153 days) before bilateral lung transplant with those for 24 CF patients who were not mechanically ventilated before transplant. CF patients ventilated pre-lung-transplant had significantly prolonged extubation time after transplant (11 vs. 4 days); however, no statistical difference between the two groups was found with regard to days until hospital discharge, FEV_1 % predicted value one year after transplant, or post-transplant survival [7]. Massard et al. evaluated 54 CF patients who underwent bilateral lung transplant, 10 of whom were mechanically ventilated for 14.5±4.5 days (range 3–42 days) before transplant. Actuarial survival at one year was 70 % for the latter group, and was no different from that for the patients not mechanically ventilated [8]. Proper selection of such patients is necessary to achieve acceptable outcomes.

Lung Allocation Score

In 2005 the Organ Procurement and Transplantation Network implemented the lung allocation score (LAS), changing the system from one primarily based on waiting list time to one allocating donor lungs on the basis of a score calculated from multiple variables. The LAS was derived from a prediction of benefit, calculated using expected one-year post-transplant survival days and expected one-year waiting-list-time survival days. The principle objective of the LAS was to reduce the number of deaths among potential and actual lung-transplant candidates aged 12 years or older [9]. Since implementation of the LAS, there has been a reduction in waiting-list mortality without a significant effect on post-transplant survival, particularly for low-LAS groups.

Thabut et al. reviewed data from the United Network for Organ Sharing (UNOS) registry and identified 704 adult CF patients on a waiting list for lung transplant from 2005 to

Table 1 Guidelines for referral (Ref. [4])

FEV_1 below 30 % predicted or a rapid decline in FEV_1—in particular for young female patients
Exacerbation of pulmonary disease requiring ICU stay
Increasing frequency of exacerbation requiring antibiotic therapy
Refractory and/or recurrent pneumothorax
Recurrent hemoptysis not controlled by embolization

2009. The main objective of the study was to assess the survival benefit of lung transplant for CF patients since LAS implementation. The cumulative incidence of lung transplant was 39.3 % (95 % CI: 35.6–42.9 %) at three months and 64.7 % (61–68.4 %) at 12 months, whereas the incidence of death during the same period for patients still on the waiting list was 8.5 % (6.4–10.6 %) at three months and 12.9 (10.3–15.5 %) at 12 months. Post-transplant survival was 96.5 % (94.7–98.2 %) at three months, 88.4 % (85.1–91.8 %) at 12 months, and 67.8 % (59.6–76.8 %) at three years. Lung transplant was associated with a 69 % reduction in risk of death (51–80 %) [10•]. For comparison, the percentage of waiting-list CF patients (n=708) dying between January 1, 1997 and December 31, 1998 was 28 % [9].

Infections

Most CF patients are colonized by or chronically infected with respiratory pathogens (e.g. *Pseudomonas aeruginosa*, Methicillin-resistant *Staphylococcus aureus*, *Burkholderia cepacia*, *Stenotrophomonas maltophilia*). Despite initial studies reporting poor post-lung-transplant outcomes for patients with multi-drug-resistant *Pseudomonas aeruginosa* compared with non-infected individuals [11], subsequent studies found that post-lung-transplant survival was not affected [12–15]. However, there may be an association between the development of bronchiolitis obliterans syndrome (BOS) and infection, and possibly even colonization, by *Pseudomonas aeruginosa* [16, 17, 18••].

Burkholderia cepacia complex species affect approximately 3–5 % of CF patients. *B. cenocepacia* (formerly known as "genomovar III") is strongly associated with increased one year post-lung-transplant mortality, with survival of infected patients being approximately 15–20 % lower at all time after lung transplant compared with that of other CF patients [19–21]. Even with adjustments to immunosuppressant drugs and aggressive antibiotic regimens, patients usually die of sepsis "cepacia syndrome" within the first few months. Many lung transplant centers regard *B. cenocepacia* as an absolute contraindication for lung transplant, although some centers have published case reports of successful outcomes [20–23]. Other *Burkholderia cepacia* complex species, excluding *B. cenocepacia*, have resulted in outcomes comparable with the ISHLT registry data.

Other common infectious colonizers and/or infectious agents associated with CF are *Aspergillus* and non-tuberculous mycobacterial (NTM) species. Approximately 20 % of CF patients are colonized with *Aspergillus* species pre-lung transplant. The presence of *Aspergillus* species has not been found to affect lung transplant outcomes; however, data suggest an increased risk of BOS and of airway complications (e.g. bronchial anastomosis infection) [24–27]. Non-tuberculous mycobacterial species are isolated from 10–15 % of CF patients, the most common being *Mycobacterium avium* complex [28, 29]. NTM have been increasingly identified in the post-lung-transplant population, with prevalence of 13.7 % in CF patients compared with 3.8–9 % in other lung transplant patients [30, 31, 32•]. The presence of NTM species has not been found to affect lung transplant outcomes [31, 32•, 33••]; however, *Mycobacterium abscessus* can pose substantial challenges post-lung transplant. *M. abscessus*' disseminated nature often contributes to diseases involving skin, soft tissues, and foreign bodies. It is not uncommon for *M. abscessus* to affect the thoracic cavity, resulting in empyema,

Table 2 Absolute contraindications (Ref. [4])

Malignancy within the past two years, with the exception of cutaneous squamous and basal cell cancers. Recommend five-year disease-free interval.
Untreatable advanced dysfunction of another major organ system (e.g. heart, kidney, or liver).
Non-curable chronic infection (e.g. human immunodeficiency virus, hepatitis B, or hepatitis C)
Significant chest wall or spinal deformity
Documented non-adherence or inability to follow through with medical therapy and/or appointments
Untreatable psychiatric or psychosocial condition
Absence of a consistent or reliable social support system
Active (or active within the last six months) substance addiction (e.g. tobacco, alcohol, or narcotics)

mediastinitis, and lung abscess. *M. abscessus* contributes to substantially more morbidity and mortality post-lung transplant than other NTM species [31, 32•]. However, isolation of *M. abscessus* during the pre-transplant evaluation process is not a contraindication for lung transplant. Eradication using a standard triple-drug regimen as recommended by American Thoracic Society guidelines should be attempted before transplant [34, 35]. Some transplant centers require smear negativity before lung transplant. Case studies of successful outcomes were reported for patients colonized with *M. abscessus* [36]. Aggressive treatment with anti-mycobacterial drugs for one year post-lung transplant is recommended. However, caution is required because of drug–drug interactions between anti-mycobacterial drugs (e.g. rifampin) and immunosuppressive agents (e.g. calcineurin inhibitors).

Diabetes

The incidence of CF-related diabetes (CFRD) has increased as more patients live longer, and it now affects approximately 19 % of adolescents and 40–50 % of adults [37]. Propensity to develop CFRD depends on gender: Sims et al. showed female patients to have a greater likelihood of having CFRD than male counterparts (OR: 12.38; CI: 2.6–59.0; P=0.002) [38]. Complications associated with CFRD include microvascular (but not macrovascular) disease, reduced lung function, and increased mortality [37, 40•, 41]. Microvascular complications are primarily related to neuropathy, microalbuminuria, and retinopathy, although to a lesser extent than seen in other diabetes populations [39]. CFRD related to post-lung-transplant outcomes is limited. Studies to date have not shown an associated increased risk of mortality [42, 43••, 44]. For patients who are not diabetic pre-lung transplant, CF is an independent risk factor for developing CFRD post-lung transplant [42, 45]. Although CFRD is not a contraindication for lung transplant, uncontrolled CFRD may be.

Gastroenterology

GI-tract manifestations of CF are an increasing cause of morbidity for post-lung transplant CF patients. Manifestations commonly seen in adult patients include gastroesophageal reflux (GERD), pancreatic insufficiency, biliary disease (e.g. cholelithiasis, biliary cirrhosis), and distal intestinal obstruction syndrome (DIOS). Colon cancer, although a significant contributor to morbidity and mortality, is a less common complication.

GERD has a prevalence of approximately 75 % to 90 % in CF patients [46, 47]; in comparison, GERD is prevalent in approximately 50 % to 75 % of lung transplant patients suffering from other causes of end-stage lung disease [48, 49]. It is hypothesized that increased risk of post-lung transplant GERD could be associated with vagal nerve injury (intra-operatively), immunosuppressive therapy, and pre-transplant diagnosis of GERD. Studies have confirmed a strong correlation between GERD and bronchiolitis obliterans syndrome (BOS). King et al. found non-acid reflux pepsin and bile salts, measured by use of esophageal impedance, to be associated with development of BOS [50]. Other studies have revealed an association between BOS and the presence of bile acids and peptins in bronchoalvealor lavage specimens [51, 52]. Proton-pump inhibitors have been revealed to reduce the acidity of gastric contents; however, they do not reduce non-acid reflux. Palmer et al. and others showed that Nissen fundoplication, a surgical intervention, halted lung allograft dysfunction caused by acid reflux [53, 54, 55•, 56]. Given the high incidence of GERD in CF patients, early recognition and implementation of therapy is prudent to support successful long-term survival.

Pancreatic insufficiency and malnutrition contribute to morbidity and mortality for CF patients. Pancreatic insufficiency affects absorption of immunosuppressive therapy (e.g. calcineurin inhibitors). Although no compelling evidence supports routine use of supplemental pancreatic enzymes, expert opinion recommends co-administration to maintain adequate enzyme levels. Malnutrition affects post-lung transplant survival of CF patients. Madill et al. revealed that a body mass index <17 kg m^{-2} was associated with a 3.7 odds ratio for risk of death within 90 days of lung transplant [57]. In contrast, Lederer et al. showed increased late mortality for underweight transplant recipients with CF, which was attributed to chronic allograft dysfunction [58]. Underweight patients and chronically ill patients have low serum albumin, and hypoalbuminemia (serum albumin <3.5 mg dL^{-1}) is a marker of inflammation. Using albumin concentration as a continuous predictor, Zisman et al. showed that patients with idiopathic interstitial pneumonia who were on the waiting list for lung transplants had a mortality hazard ratio of 1.79 associated with each 0.5 mg dL^{-1} reduction in serum albumin concentration [59]. Similarly, Baldwin et al. found that, compared with other diseases including chronic obstructive pulmonary disease and idiopathic pulmonary fibrosis, post-lung-transplant CF patients with hypoalbuminemia had the strongest association with significantly reduced one-year and overall survival [60••]. Overall, although being underweight (or severely malnourished) is not an absolute contraindication, aggressive measures should be taken to improve nutritional status before lung transplant.

Distal intestinal obstruction syndrome (DIOS) affects approximately 10–20 % of CF patients post-lung transplant, almost exclusively affecting patients with pancreatic insufficiency [61, 62]. Precipitating factors include narcotic use, poor oral intake and/or dehydration shortly after transplant. To avoid

the need for surgical intervention, active measures, including aggressive bowel regimens, should be instituted before onset.

Pre-transplant CF-related liver disease is the third most common cause of mortality of CF patients. However, serious liver disease associated with liver cirrhosis and portal hypertension resulting in synthetic dysfunction is prevalent in 10 % of CF patients only [63]. Despite evidence of CF-associated liver cirrhosis with preserved synthetic function, Nash et al. reported that carefully selected CF patients can tolerate lung transplant, with outcomes comparable with those for CF patients without CF-related liver disease [64•]. Regarding combined lung–liver transplant, Desai et al. reported outcomes comparable with those for isolated lung transplant [65]. Actuarial survival for combined lung–liver transplant for one, three, and five years was 72 %, 61.4 %, and 61.4 %, respectively. Similar outcomes were reported by other institutions [66]. Combined transplant outcomes are probably comparable with those for isolated lung transplant because of increased scrutiny of recipient selection criteria and young recipient age.

Sinus Disease

Sinusitis affects most CF patients. Organisms identified within the sinus tract are identical with those of the lower respiratory tract. Leung et al. performed a retrospective chart review of all CF patients who underwent heart–lung and lung transplant at Stanford Medical Center between 1988 and 2005, assuming that pre-lung-transplant surgical sinus intervention would lead to reduced bacterial seeding of the transplanted lungs. For 87 % of patients re-colonization with *Pseudomonas* occurred, and an overall survival benefit was not evident [67].

Malignancy

Risk of developing malignancy is increasing as the survival of post-lung transplant patients continues to improve. The ISHLT registry reports cumulative malignancy risk for one-year, three-year, and five-year survivors to be 3.5 %, 14.1 %, and 27.2 %, respectively [1•]. In a retrospective cohort study of 93 lung transplant recipients with CF, Saueressig et al. revealed an 8.6 % risk of developing post-transplant lymphoproliferative disease during a median time of six months (range 3–19 months) for seronegative CF patients with Epstein–Barr virus and human herpes virus (types 1, 2, 3, 6, and 8) [68••]. Colorectal cancer is the third most common malignancy diagnosed in the general population of the US. In a recent study, Maisonneuve et al. prospectively obtained data covering a 20-year period from the US Cystic Fibrosis Foundation Patient registry. Post-lung transplant, they found an unexpectedly high risk of digestive tract cancers (19 observed vs. 1.1 expected; 95 % CI: 10.7–26.5), particularly cancer of the colon (11 observed vs. 0.4 expected; 95 % CI: 15.8–52.2). One hypothesis suggests the combination of underlying bowel cancer risk and immunosuppressant therapy after lung transplant leads to a higher incidence for this population [69••, 70••].

Conclusions

The leading cause of death of CF patients is respiratory failure. Until improved medical therapy brings about a substantial reduction in respiratory failure, lung transplant remains a treatment option for CF patients. Despite the multiple co-morbidities associated with increased morbidity and mortality in CF, long-term outcomes for CF patients continue to be superior to those for patients with other lung diseases amenable to transplant. Possible areas for future research to improve transplant outcomes include surgical technique, organ procurement and preservation, and post-operative management in the intensive care unit.

Compliance with Ethics Guidelines

Conflict of Interest David Weill declares that he has no conflict of interest.

Kapil Patel declares that he has no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

References

Papers of particular interest, published recently, have been highlighted as:

- • Of importance
- •• Of major importance

1. • Christie JD, Edwards LB, Kucheryavaya AY, et al. Registry of the International Society for Heart and Lung Transplantation: 29th adult lung and heart-lung transplant report–2012. J Heart Lung Transplant. 2012;31:1073–86. *Up dated registry for lung transplantation*.
2. Rich DP, Anderson MP, Gregory RJ, et al. Expression of cystic fibrosis transmembrane conductance regulator corrects defective chloride channel regulation in cystic fibrosis airway epithelial cells. Nature. 1990;27:358–63.
3. Cystic Fibrosis Foundation. Patient registry 2011 annual report. Bethesda, MD.
4. Orens JB, Estenne M, Arcasoy S, et al. International guidelines for the selection of lung transplant candidates: 2006 update—a consensus report from the Pulmonary Scientific Council of the International

Society for Heart and Lung Transplantation. J Heart Lung Transplant. 2006;25:745–55.
5. Kerem E, Reisman J, Corey M, et al. Prediction of mortality in patients with cystic fibrosis. N Engl J Med. 1992;326:1187–91.
6. Mayer-Hamblett N, Rosenfeld M, Emerson J, et al. Developing cystic fibrosis lung transplant referral criteria using predictors of 2-year mortality. Am J Respir Crit Care Med. 2002;166:1550–5.
7. Bartz RR, Love RB, Leverson GE, et al. Pretransplant mechanical ventilation and outcome in patients with cystic fibrosis. J Heart Lung Transplant. 2004;22:433–8.
8. Massard G, Shennib H, Metras D, et al. Double-lung transplantation in mechanically ventilated patients with cystic fibrosis. Ann Thorac Surg. 1993;55:1087–92.
9. Egan TM, Murray S, Bustami RT, et al. Development of the new lung allocation system in the United States. Am J Transplant. 2006;6:1212–27.
10. • Thabut G, Christie JD, Mal H, et al. Survival benefit of lung transplant for cystic fibrosis since lung-allocation-score implementation. Am J Respir Crit Care Med. 2013; In press *Recent work demonstrating the effect of the Lung Allocation Score for CF patients.*
11. Griffith BP, Hardesty RL, Armitage JM, et al. A decade of lung transplantation. Ann Surg. 1993;218:310–20.
12. Aris RM, Gilligan PH, Neuringer IP, et al. The effects of panresistant bacteria in cystic fibrosis patients on lung transplant outcome. Am J Respir Crit Care Med. 1997;155:1699–704.
13. Nunley DR, Grgurich W, Iacono AT, et al. Allograft colonization and infections with *Pseudomonas* in cystic fibrosis lung transplant recipients. Chest. 1998;113:1235–43.
14. Dobbin C, Maley M, Harkness J, et al. The impact of pan-resistant bacterial pathogens on survival after lung transplantation in cystic fibrosis: results from a single large referral center. J Hosp Infect. 2004;56:277–82.
15. Hadjiliadis D, Steele MP, Chaparro C, et al. Survival of lung transplant recipients with cystic fibrosis harboring panresistant bacteria other than *B cepacia*, compared to patients harboring sensitive bacteria. J Heart Lung Transplant. 2007;26:834–8.
16. Botha P, Archer L, Anderson RL, et al. *Pseudomonas aeruginosa* colonization of the allograft after lung transplantation and the risk of bronchiolitis obliterans syndrome. Transplantation. 2008;85:771–4.
17. Vos R, Vanaudenaerde BM, De Vleeschauwer SI, et al. De novo or persistent pseudomonal airway colonization after lung transplantation: importance for bronchiolitis obliterans syndrome? Transplantation. 2008;86:624–5.
18. •• Gregson AL, Wang X, Weigt SS, et al. Interaction between *Pseudomonas* and CXC chemokines increases risk of bronchiolitis obliterans syndrome and death in lung transplantation. Am J Respir Crit Care Med. 2013;187:518–26. *Pseudomonas organisms probably contribute to an increased risk of developing bronchiolitis obliterans syndrome with colonization*.
19. Aris RM, Routh JC, KiPuma JJ, et al. Lung transplantation for cystic fibrosis patients with *Burkholderia cepacia* complex: survival linked to genomovar type. Am J Respir Crit Care Med. 2001;164:2102–6.
20. Chaparro C, Maurer J, Gutierrez C, et al. Infection with *Burkholderia cepacia* in cystic fibrosis: outcome following lung transplantation. Am J Respir Crit Care Med. 2001;163:43–8.
21. De Soyza A, Meachery G, Hester KL, et al. Lung transplantation for patients with cystic fibrosis and *Burkholderia cepacia* complex infection: a single-center experience. J Heart Lung Transplant. 2010;29:1395–404.
22. Nash EF, Coonar A, Kremer R, et al. Survival of *Burkholderia cepacia* sepsis following lung transplantation in recipients with cystic fibrosis. Transpl Infect Dis. 2010;12:551–4.
23. Olland A, Falcoz PE, Kessler R, et al. Should cystic fibrosis patients infected with *Burkholderia cepacia* complex be listed for lung transplantation? Interact Cardiovasc Thorac Surg. 2011;13:631–4.
24. Flume PA, Egan TM, Paradowski LJ, et al. Infectious complications of lung transplantation. Impact of cystic fibrosis. Am J Respir Crit Care Med. 1994;149:1601–7.
25. Nunley DR, Ohori P, Grgurich WF, et al. Pulmonary aspergillus in cystic fibrosis lung transplant recipients. Chest. 1998;114:1321–9.
26. Helmi B, Love RB, Welter D, et al. Aspergillus infection in lung transplant recipients with cystic fibrosis: risk factors and outcomes comparison to other types of transplant recipients. Chest. 2003;123:800–8.
27. Weigt SS, Elashoff RM, Huang C, et al. Aspergillus colonization of the lung allograft is a risk factor for bronchiolitis obliterans syndrome. Am J Transplant. 2009;9:1903–11.
28. Olivier K, Weber DJ, Lee JH, et al. Nontuberculous *mycobacteria*. II: nested-cohort study of impact on cystic fibrosis lung disease. Am J Respir Crit Care Med. 2003;167:835–40.
29. Roux AL, Catherinot E, Ripoll F, Jean-Louis Herrmann for the OMA Group, et al. Multicenter study of prevalence of nontuberculous *mycobacteria* in patients with cystic fibrosis in France. J Clin Microbiol. 2009;47:3467–70.
30. Bonvillain RW, Valentine VG, Lombard G, et al. Post-operative infections in cystic fibrosis and non-cystic fibrosis patients after lung transplantation. J Heart Lung Transplant. 2007;26:890–7.
31. Chalermskulrat W, Sood N, Neuringer IP, et al. Non-tuberculous *mycobacteria* in end stage cystic fibrosis: implications for lung transplantation. Thorax. 2006;61:506–13.
32. • Knoll BM, Kappagoda S, Gill RR, et al. Non-tuberculous *mycobacterial* infection among lung transplant recipients: a 15-year cohort study. Transpl Infect Dis. 2012;14:452–60. *This study revealed the increasing prevalence of non-tuberculous mycobacteria in CF patients. Despite the increasing prevalence, non-tuberculous mycobacteria have not affected post-lung transplant outcomes*.
33. •• Leung JM, Olivier KN. Nontuberculous *Mycobacteria* in patients with cystic fibrosis. Semin Respir Crit Care Med. 2013;34:124–34. *An overview of the clinical management of nontuberculous Mycobacteria in CF patients*.
34. Watkins RR, Lemonovich TL. Evaluation of infections in the lung transplant patient. Curr Opin Infect Dis. 2012;25:193–8.
35. Griffith DE, Aksamit T, Brown-Elliot BA, et al. An official ATS/IDSA statement: diagnosis, treatment, and prevention of nontuberculous mycobacterial diseases. Am J Respir Crit Care Med. 2007;175:367–416.
36. Gilljam M, Schersten H, Silverborn M, et al. Lung transplantation in patients with cystic fibrosis and *Mycobacterium abscessus* infection. J Cyst Fibros. 2010;9:272–6.
37. Moran A, Dunitz J, Nathan B, et al. Cystic fibrosis-related diabetes: current trends in prevalence, incidence, and mortality. Diabetes Care. 2009;32:1626–31.
38. Sims EJ, Green MW, Mehta A. Decreased lung function in female but not male subjects with established cystic fibrosis-related diabetes. Diabetes Care. 2005;28:1581–7.
39. Schwarzenberg SJ, Thomas W, Olsen TW, et al. Microvascular complications in cystic-fibrosis-related diabetes. Diabetes Care. 2007;30:1056–61.
40. • Moran A, Becker D, Casella SJ, et al. Epidemiology, pathophysiology, and prognostic implications of cystic fibrosis-related diabetes. Diabetes Care. 2010;33:2677–83. *An overview of the epidemiology and pathophysiology of CFRD, and the effect of CFRD on lung function and mortality.*
41. Miller RJ, Tildesley HD, Wilcox PG, et al. Sex disparities in effects of cystic fibrosis-related diabetes on clinical outcomes: a matched study. Can Respir J. 2008;15:291–4.
42. Hadjiliadis D, Madill J, Chaparro C, et al. Incidence and prevalence of diabetes mellitus in patients with cystic fibrosis undergoing lung transplantation before and after lung transplantation. Clin Transplant. 2005;19:773–8.
43. •• Hofer M, Schmid C, Benden C, et al. Diabetes mellitus and survival in cystic fibrosis patients after lung transplantation. J Cyst

Fibros. 2012;11:131–6. *This study revealed improved 1 and 5-year survival post-transplant with DM. No effect on the development of bronchiolitis obliterans syndrome*.
44. Valour F, Brault C, Abbas-Chorfa F, et al. Outcome of cystic fibrosis-related diabetes two years after lung transplantation. Respiration. 2012; In press.
45. Ye X, Kuo H-T, Sampaio MS, et al. Risk factors for development of new-onset diabetes mellitus after transplant in adult lung transplant recipients. Clin Transplant. 2011;25:885–91.
46. Mendez BM, Davis CS, Weber C, et al. Gastroesophageal reflux disease in lung transplant patients with cystic fibrosis. Am J Surg. 2012;204:e21–6.
47. Button BM, Roberts S, Kotsimbos TC, et al. Gastroesophageal reflux (symptomatic and silent): a potentially significant problem in patients with cystic fibrosis before and after lung transplantation. J Heart Lung Transplant. 2005;24:1522–2529.
48. Hadjiliadis D, Davis RD, Steele MP, et al. Gastroesophageal reflux disease in lung transplant recipients. Clin Transplant. 2003;17:363–8.
49. Hoppo T, Jarido V, Pennathur A, et al. Antireflux surgery preserves lung function in patients with gastroesophageal reflux disease and end-stage lung disease before and after lung transplantation. Arch Surg. 2011;146:1041–7.
50. King BJ, Iyer H, Leidi AA, Carby MR. Gastroesophageal reflux in bronchiolitis obliterans syndrome: a new perspective. J Heart Lung Transplant. 2009;28:870–5.
51. D'Ovidio F, Mura M, Tsang M, et al. Bile acid aspiration and the development of bronchiolitis obliterans after lung transplantation. J Thorac Cardiovasc Surg. 2005;129:1144–52.
52. Blondeau K, Mertens V, Vanaudenaerde BA, et al. Gastro-oesophageal reflux and gastric aspiration in lung transplant patients with or without chronic rejection. Eur Repir J. 2008;31:707–13.
53. Palmer SM, Miralles AP, Howell DN, et al. Gastroesophageal reflux as a reversible cause of allograft dysfunction after lung transplantation. Chest. 2000;118:1214–7.
54. Lau CL, Palmer SM, Howell DN, et al. Laparoscopic antireflux surgery in the lung transplant population. Surg Endosc. 2002;16:1674–8.
55. • Fisichella PM, Davis CS, Lowery E, et al. Pulmonary immune changes early after laparoscopic antireflux surgery in lung transplant patients with gastroesophageal reflux disease. J Surg Res. 2012;177:e65–73. *Demonstrated that post laparoscopic antireflux surgery altered the inflammatory cells in bronchoalveolar lavage fluid*.
56. Hayes Jr D, Kirkby S, S McCoy K, et al. Reduction of lipid-laden macrophages index after laparoscopic Nissen fundoplication in cystic fibrosis patients after lung transplantation. Clin Transplant. 2013;27:121–5.
57. Madill J, Gutierrez C, Grossman J, et al. Nutritional assessment of the lung transplant patient: body mass index as a predictor of 90-day mortality following transplantation. J Heart Lung Transplant. 2001;20:288–96.
58. Lederer DJ, Wilt JS, D'Ovidio F, et al. Obesity and underweight are associated with an increased risk of death after lung transplantation. Am J Respir Crit Care Med. 2009;180:887–95.
59. Zisman DA, Kawut SM, Lederer DJ, et al. Serum albumin concentration and waiting list mortality in idiopathic interstitial pneumonia. Chest. 2009;135:929–35.
60. •• Baldwin MR, Arcasoy SM, Shah A, et al. Hypoalbuminemia and early mortality after lung transplantation: a cohort study. Am J Transplant. 2012;12:1256–67. *For CF and interstitial lung disease patients the association between low serum albumin and post-transplant survival was strongest*.
61. Gilljam M, Chaparro C, Tullis E, et al. GI complications after lung transplantation in patients with cystic fibrosis. Chest. 2003;123:37–41.
62. Morton JR, Ansari N, Glanville AR, et al. Distal intestinal obstruction syndrome (DIOS) in patients with cystic fibrosis after lung transplantation. J Gastrointest Surg. 2009;13:1448–53.
63. Rowland M, Gallagher CG, O'Laoide R, et al. Outcome in cystic fibrosis liver disease. Am J Gastroenterol. 2011;106:104–9.
64. • Nash EF, Volling C, Gutierrez CA, et al. Outcomes of patients with cystic fibrosis undergoing lung transplantation with and without cystic fibrosis-associated liver cirrhosis. Clin Transplant. 2012;26:34–41. *CF patients may be considered for lung transplantation in the setting of known cirrhosis without synthetic dysfunction from CF-related liver disease*.
65. Desai CS, Gruessner A, Habib S, et al. Survival of cystic fibrosis patients undergoing liver and liver-lung transplantations. Transplant Proc. 2013;45:290–2.
66. Barshes NR, DiBardino DJ, McKenzie ED, et al. Combined lung and liver transplantation: the United States experience. Transplantation. 2005;80:1161–7.
67. Leung MK, Rachakonda L, Weill D, Hwang PH. Effects of sinus surgery on lung transplantation outcomes in cystic fibrosis. Am J Rhinol. 2008;22:192–6.
68. •• Saueressig MG, Boussaud V, Amrein C, et al. Risk factors for post-transplant lymphoproliferative disease in patients with cystic fibrosis. Clin Transplant. 2011;25:E430–6. *Risk factors for developing PTLD in CF patients are EBV-negative and human herpesvirus negative*.
69. •• Maisonneuve P, Marshall BC, Knapp EA, Lowenfels AB. Cancer risk in cystic fibrosis: a 20-year nationwide study from the United States. J Natl Cancer Inst. 2013;105:122–9. *This study revealed an overall low risk of cancer for CF patients. However, post-transplantation there is a significantly increased risk of developing digestive tract cancers*.
70. •• Meyer KC, Francois ML, Thomas HK, et al. Colon cancer in lung transplant recipients with CF: increased risk and results of screening. J Cyst Fibros. 2011;10:366–9. *Colonoscopic screening is extremely important for CF patients in comparison with non-CF recipients*.