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Lung Transplantation for Cystic Fibrosis: Results, Indications, Complications, and Controversies

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Abstract

Survival in patients with cystic fibrosis (CF) has improved dramatically over the past 30 to 40 years, with mean survival now approximately 40 years. Nonetheless, progressive respiratory insufficiency remains the major cause of mortality in CF patients, and lung transplantation (LT) is eventually required. Timing of listing for LT is critical, because up to 25 to 41% of CF patients have died while awaiting LT. Globally, approximately 16.4% of lung transplants are performed in adults with CF. Survival rates for LT recipients with CF are superior to other indications, yet LT is associated with substantial morbidity and mortality (~50% at 5-year survival rates). Myriad complications of LT include allograft failure (acute or chronic), opportunistic infections, and complications of chronic immunosuppressive medications (including malignancy). Determining which patients are candidates for LT is difficult, and survival benefit remains uncertain. In this review, we discuss when LT should be considered, criteria for identifying candidates, contraindications to LT, results post-LT, and specific complications that may be associated with LT. Infectious complications that may complicate CF (particularly *Burkholderia cepacia* spp., opportunistic fungi, and nontuberculous mycobacteria) are discussed.

Keywords

lung transplant; cystic fibrosis; *Burkholderia cepacia* spp

Survival in patients with cystic fibrosis (CF) has improved dramatically over the past 30 to 40 years.^{1–4} Mean survival in the United States increased from 16 years in 1970 to approximately 38 years by 2005.^{2,5} In the United Kingdom, median survival was 41.4 years as of 2011.⁴ Successive cohorts are living longer, and it has been estimated that life expectancy among CF patients born after 2000 will exceed 50 years.⁶ Notwithstanding these favorable trends, progressive respiratory insufficiency remains the major cause of mortality in CF patients, and lung transplantation (LT) is eventually required.^{7,8} Timing of listing for LT is critical, because up to 25 to 41% of CF patients have died while awaiting LT.^{9–12}

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Lung Transplantation for Cystic Fibrosis

In 2014, the International Society for Heart and Lung Transplantation (ISHLT) registry published outcome data regarding > 47,000 adult lung transplant recipients (LTRs) and > 3,770 adult heart–lung transplant (HLT) recipients performed worldwide up to June 30, 2013.¹³ CF accounted for approximately 16.4% of LT recipients; survival rates for LT recipients from January 1990 to June 2012 were superior for CF patients (~60% at 5 years) compared with LTR with other diagnoses (~50% at 5 years); *conditional* median survival *for patients surviving at least 3 months* was 10.0 years among CF patients compared with 6.2 years for chronic obstructive pulmonary disease ($p < 0.05$) and 5.9 years for interstitial lung disease ($p < 0.05$).¹³ This difference undoubtedly reflects in part the younger age of CF transplant recipients. Importantly, several studies have reported improvements in quality of life (QOL) among CF patients following LT.^{14–17}

Lung Transplantation for Cystic Fibrosis (History)

In 1983, the first combined HLT was performed for CF.¹⁸ In the mid-1980s, combined HLT (en bloc or the domino procedure) was the procedure of choice for CF.^{18–20} However, by the mid to late 1990s, bilateral sequential lung transplant became the standard procedure for CF patients.^{21–27} Subsequent refinements included the “clamshell” incision and bilateral anterior thoracotomies without dividing the sternum.^{28,29} Because of the high mortality among CF patients in respiratory failure awaiting LT, Starnes et al developed living-donor lobar LT as an alternative to cadaveric LT.^{30–33} However, this operation is rarely done and is only performed in a few centers.^{34–37} Combined lung–liver^{38,39} or lung–renal⁴⁰ transplants have been done in CF patients, but will not be further discussed here.

When Should CF Patients Be Listed for Lung Transplant?

The decision to list CF patients for LT is complex and needs to take into account not only the severity of the pulmonary disease but also the rate of change in pulmonary function tests, frequency of exacerbations, nutritional status, comorbidities, and colonization or infection with key pathogens. Guidelines published by the ISHLT in 2006⁴¹ recommended referral to a transplant center when CF patients met the criteria depicted in Table 1: (1) forced expiratory volume in 1 second (FEV_1) < 30%; rapid decline in FEV_1 , particularly in young female patients; (2) exacerbation of pulmonary disease requiring an intensive care unit (ICU) stay; (3) increasing frequency of exacerbations requiring antibiotic therapy; (4) refractory and/or recurrent pneumothorax; and (5) recurrent hemoptysis not controlled by embolization. Further, referral for LT should be considered for any of the following criteria: (1) oxygen-dependent respiratory failure; (2) hypercapnia; and (3) pulmonary hypertension (PH).⁴¹ Those guidelines were based on expert opinion, but lacked firm evidence. In the sections that follow, we discuss specific criteria and recommendations for LT in CF patients.

Contraindications to Lung Transplant

In 2006, the ISHLT iterated a variety of contraindications to LT for both CF and non-CF patients.⁴¹ Absolute contraindications included malignancy within 2 years; untreatable advanced dysfunction of another major organ system; infection with human

immunodeficiency virus; hepatitis B with positive surface antigen; hepatitis C with biopsy-proven liver disease; inability to adhere to complex medical plan; and substance addiction within 6 months. Numerous other relative contra-indications (relative or center specific) were also cited. These global and comprehensive guidelines are beyond the scope of this article.

Predicting Survival in Cystic Fibrosis and Need for Lung Transplant

Predicting survival among CF patients is difficult, as no single parameter can predict prognosis with accuracy.^{2,9} Which candidates are appropriate for LT is controversial.^{7,42–44} Pulmonary functional parameters^{11,45} and annual rate of decline have been useful to identify appropriate timing for LT.⁴⁶ The FEV₁ has been the most often used functional variable to predict prognosis. In a sentinel article in 1992, Kerem et al reported that FEV₁ < 30% in CF patients predicted a 2-year mortality of approximately 50%.⁴⁵ In that study, other predictors of a worse prognosis included paO₂ < 50; paCO₂ > 55 mm Hg; female gender; and age < 18 years.⁴⁵ In another single-center study, a cutoff value of FEV₁ of < 30% predicted was not a reliable predictor of high risk of death within 2 years; the annual rate of decline of percent predicted FEV₁ was a better parameter to identify those patients at high risk for death.⁴⁷ Similarly, Augarten et al reported that FEV₁ did not predict mortality, whereas *rapid rate of decline* of FEV₁ and age < 15 years predicted increased mortality.⁴⁸ In retrospective studies, hypercapnea,^{49,50} PH,^{12,49–51} and reduced walk distance on 6-minute walk tests⁵² were predictive of higher mortality in CF patients on the waiting list for LT.^{49,50}

Mayer-Hamblett et al developed a model to identify the best clinical predictors of 2-year mortality among patients with CF (data gleaned from the Cystic Fibrosis Foundation Patient Registry [CFFPR] comprising 14,572 patients who were 6 years of age or older in 1996).⁵³ By multivariate logistic regression, age, height, FEV₁, respiratory microbiology, number of hospitalizations for pulmonary exacerbations, and number of home intravenous antibiotic courses were all significant predictors of 2-year mortality. Interestingly, this well-fitting model provided no better diagnostic accuracy than the simpler FEV₁ criterion. Both had high negative predictive values (98 and 97%, respectively) but only modest positive predictive values (33 and 28%, respectively).

Belkin et al retrospectively reviewed 343 CF patients listed for LT at four academic medical centers to identify risk factors for death while awaiting LT.⁴² Univariate and multivariate survival analyses were performed using Cox regression. By univariate analyses, FEV₁ 30% predicted (hazards ratio [HR], 3.8), paCO₂ 50 mm Hg (HR, 1.85), and shorter height (HR, 1.8) were associated with an increased risk of death. Referral from an accredited CF center was associated with a lower risk (HR, 0.53). In the final multivariate model, referral from an accredited CF center (HR, 0.5) and listing year after 1996 (HR, 0.4) both were associated with a lower risk of death. By contrast, FEV₁ 30% predicted (HR, 6.8), paCO₂ 50 mm Hg (HR, 6.9), and use of a nutritional intervention (HR, 2.3) were associated with increased risk. Patients with FEV₁ > 30% predicted had a higher risk of death only when their paCO₂ was 50 mm Hg (HR, 7.0), while the increased risk of death with FEV₁ 30% was not further influenced by the presence of hypercapnia.

One retrospective review of 69 adults with CF hospitalized for severe pulmonary exacerbations between January 1997 and June 2001 cited 1-year survival rates of 52% (12 of 23) requiring ICU and 91% (42/46) *not* requiring ICU care.⁵⁴ In the univariate analysis, factors predictive of death were colonization with *Burkholderia cepacia*, rapid decline in FEV₁ before admission, and severity of exacerbations (severity of hypoxemia and hypercapnia, simplified acute physiology score II and logistic organ dysfunction [LOD] scores, requirement for noninvasive mechanical ventilation (MV), and hospitalization in the ICU). In the multivariate analysis, prior colonization with *B. cepacia*, the severity of hypoxemia at admission, and hospitalization in the ICU were predictive of mortality.

PH is an independent risk factor for mortality in CF patients with advanced lung disease.⁵¹ Hayes et al reviewed 2,781 CF patients on the United Network for Organ Sharing (UNOS) lung transplant waiting list from 1987 to 2013.⁵¹ Mild PH was defined as mean pulmonary artery pressure (PAP) > 25 but < 35 mm Hg; severe PH was defined as mean PAP ≥ 35 mm Hg. Univariate Cox analysis of 2,100 patients found significant differences in survival for mild PH (HR 1.75, $p < 0.001$) and severe PH (HR 2.30, $p < 0.001$). Multivariate Cox models among 687 patients found an increased risk for death with mild PH (HR 1.757, $p < 0.001$) and severe PH (HR 2.284, $p < 0.001$). Cox regression stratified on matched pairs of PH cases and control subjects confirmed the increased risk of death for mild PH (HR 1.919, $p = 0.001$) and severe PH (HR 4.167, $p = 0.002$). Review of the UNOS database identified 831 CF patients receiving LTs from 2005 to 2011 in the United States who had right heart catheterization data available.⁵⁵ Importantly, the presence or severity of PH *pre*-LT did not influence *post*-LT survival (median survival *post*-LT of 84.4 months in CF patients with PH compared with 67.1 months in CF patients *without* PH [$p = 0.33$]).⁵⁵

Issues Prior to LT in Cystic Fibrosis Patients That May Impact Post-LT Survival

Prior Thoracic Surgery and Pleural Space Adhesions

Complications of LT in the perioperative period include bleeding, diaphragmatic paralysis or paresis, anastomotic stenosis or dehiscence, primary graft failure, pulmonary edema, mediastinitis, and infection.²⁵ Pneumothoraces complicate CF in approximately 19% of patients (lifetime risk)⁵⁶ and many CF patients have undergone surgical procedures (e.g., thoracostomy tubes, surgical pleurodesis, pleurectomy, etc.) prior to LT. Furthermore, chronic suppurative infections may lead to extensive adhesions and marked distortion of the alveolar architecture and pleural/parenchymal interface. Sequela of thoracic surgery and extensive adhesions increase the complexity of removal of the native CF lungs, and may predispose to bleeding. In the early experience of LT, high morbidity and mortality was observed as a result of pleural hemorrhage.⁵⁷ However, in one retrospective study from the United Kingdom, 16 CF patients with previous pneumothoraces later underwent LT.⁵⁸ Among early outcome measures, no differences were noted in clinically important parameters (i.e., the use of intraoperative blood products, operative time, surgical outcome, or mortality) compared with CF patients with no history of pneumothorax ($n = 16$) or 16 nonbronchiectatic patients with no history of pneumothorax.⁵⁸ In a single-center study of 69 LT recipients (all diagnoses), morbidity and mortality were not statistically different among

patients who had a previous thoracic procedures or chest tube placement compared with control patients.⁵⁹ However, a statistically significant increase in the number of blood products used was observed in patients with previous thoracic surgical procedures but not with patients having had previous chest tubes. When the data were reanalyzed with respect to the use of cardiopulmonary (CP) bypass, patients requiring bypass had a markedly poorer outcome that reached statistical significance in all of the parameters studied (i.e., hospital death, incidence of major complications, length of intubation, hospital stay, incidence of bleeding, and number of blood products used). With improvements in surgical techniques and meticulous intraoperative management, LT can be performed even in CF patients with prior surgical procedures including pleurectomy.⁶⁰ Dusmet et al compared 18 LT recipients (all indications) with previous intrapleural procedures compared with 18 LTRs *without* prior surgery involving the pleural space.⁶¹ There was no statistically significant trend for the operating time, blood loss, transfusion requirements, time intubated, or ICU stay to be greater in the study population than in the controls. However, nine patients with “major” intrapleural procedures (i.e., fusion of the pleural space or extensive adhesions) were younger, required longer CP bypass, and had a longer ICU stay. At 6- and 12-months, FEV₁ measurements were similar among the patients with *major* previous intrapleural procedures ($n = 9$), patients with *minor* previous intrapleural procedures ($n = 9$), or the controls ($n = 18$). Hence, LT can be performed even in CF patients with prior surgical procedures including pleurectomy.⁶⁰

Impact of Mechanical Ventilation Pretransplant on Survival

The need for pretransplant MV in CF patients was associated with worse short-term outcomes and higher 1-year mortality rates,^{62,63} but others found no impact of need for MV on survival rates post-LT.^{64,65} In one study, 18 children with CF requiring MV prior to LT were compared with 18 CF LTRs not requiring MV prior to LT.⁶² The need for MV pre-LT was associated with worse short- and long-term outcomes: that is, increased incidence of early graft dysfunction ($p = 0.01$); prolonged MV (34.1 vs. 5 days, $p = 0.009$); prolonged stay in the pediatric ICU (35.4 vs. 8.1 days, $p = 0.01$); worse 1-year mortality post-LT (221.6 vs. 335.2 days, $p = 0.021$). In another study, 104 admissions to the ICU from 1996 to 2006 among 48 adult CF patients were reviewed.⁶³ Among 17 patients with reversible conditions, 16 survived up to 10 years from ICU admission. Among 31 patients with acute-on-chronic respiratory failure, 23 (74%) died of respiratory failure. In that subgroup, 17 of 18 patients requiring MV died within 90 days. Hence, the need for MV is associated with a worse prognosis, but patients with underlying reversible conditions may have prolonged survival. In another study of 42 CF patients admitted to the ICU for acute respiratory failure from 1990 to 1998,⁶⁶ 23 (55%) survived to ICU discharge. Importantly, 17 received LTs, 14 of whom were alive at 1 year. Among the other six ICU survivors who were not transplanted, three were alive and three had died at 1 year. Other centers have reported acceptable results in CF patients requiring MV prior to LT.^{25,65,67} Mason et al reviewed 15,934 LT recipients (all indications) from the UNOS database from October 1987 to January 2008; 586 LTRs had required MV and 51 required extracorporeal membrane oxygenation (ECMO) support prior to LT.⁶⁸ Differences between nonsupport and those on MV or ECMO were expressed as 2 propensity scores for use in comparing risk-adjusted

survival post-LT. Unadjusted survival rates at 1, 6, 12, and 24 months were as follows: 83, 67, 62, and 57% for MV; 72, 53, 50, and 45% for ECMO; 93, 85, 79, and 70% for unsupported patients, respectively. Recipients on MV were younger, had lower vital capacity, and had diagnoses other than emphysema. Recipients on ECMO were younger, had higher body mass index (BMI), and had diagnoses other than CF/bronchiectasis.⁶⁸ In the adjusted analysis accounting for these variables, survival remained worse after LT for patients on MV or ECMO.

Singer et al conducted a similar analysis of the UNOS database, but limited to the current era of lung allocation score (LAS)-based lung allocation⁶⁹. In this study of subjects transplanted between 2005 and 2010, 419 LTRs who required MV prior to transplant were compared with an equal number of propensity-matched control recipients not on MV. MV was associated with decreased overall survival, with cumulative survival at 6 months, 1, 2, and 3 years as follows: 76, 68, 61, and 56% for MV patients; 86, 80, 71, and 60% for non-MV patients. Once patients had survived to 6 months, there was no significant difference between MV and non-MV recipients (1-, 2-, and 3-year survival 90, 80, and 73% for MV; 94, 84, and 76% for non-MV). Interestingly, the subgroup of patients with CF who required MV had a significantly higher risk of death at 6 months as compared with the rest of the MV cohort (hazard ratio [HR] 5.1 for CF, 1.9 for overall cohort). Comparable to results seen in the overall cohort, after 6 months post-LT, the risk of death in CF patients was not affected by pretransplant MV status.

In summary, in both the pre-LAS and post-LAS eras of organ allocation, pretransplant MV support is associated with a higher risk of early mortality but no increase in longer-term mortality. Nonetheless, survival is not dismal, and neither MV nor ECMO are absolute contraindications for LT.

Extracorporeal Membrane Oxygenation Support as a Bridge to Lung Transplantation

ECMO may have a role for CF patients with end-stage respiratory failure as a bridge to LT (Fig. 1).^{70–75} Traditionally, ECMO required cannulation of at least one femoral vessel, necessitating immobilization. However, the use of a dual-lumen single cannula allows ambulatory venovenous ECMO, and can be done in awake, spontaneously breathing patients.^{75–80} French investigators performed ECMO as a bridge to LT in 36 patients from 2007 to 2011.⁷³ Among 20 patients with CF, all survived ECMO and were successfully transplanted; 2-year survival rate was 71.0%; lower survival rates were noted with other indications.⁷³ ECMO may be efficacious as a bridge to LT, but has serious potential complications (e.g., bleeding, coagulopathy, strokes, ischemia, infection), is expensive, logistically difficult, requires a team of highly trained and experienced individuals, and is only available in limited centers. Randomized, controlled trials are lacking, and appropriate indications for ECMO are still being developed.

Survival of Cystic Fibrosis Patients Following Lung Transplant

Survival after LT in CF patients is superior to LT performed for other indications as measured by either median survival (8.3 years for CF; 5.7 years for all transplants) or median survival conditional on survival to 1 year (10.5 years for CF; 7.9 years for all transplants).¹³ Leading causes of post-LT mortality evolve with time after transplantation. Within the first month, primary graft dysfunction, acute infections, and technical problems are the major causes of death.¹³ Infection continues to be a major driver of mortality throughout the posttransplant course, and is the leading cause of mortality between 1 month and 1 year post-LT, accounting for approximately 35% of deaths during that time period.¹³ Beyond the first year post-LT, bronchiolitis obliterans and other forms of graft failure cause almost 50% of deaths, with infections accounting for approximately 20%.^{2,13} Malignancy is rare within the first year post-LT, but increases to approximately 15% of deaths after 5 years.¹³ Immunosuppression in CF LTRs is generally similar to other indications. In a recent review of 1,721 CF receiving LTs in the United States from 2001 to 2012, survival was better in patients receiving induction therapy with monoclonal antibodies (median survival, 93.8 months) compared with no induction (median survival, 61.8 months) ($p < 0.001$).⁸¹

Does Lung Transplantation Confer a Survival Advantage in Cystic Fibrosis?

Although LT undoubtedly is life-saving in selected patients with CF and severe respiratory failure, the overall survival benefit of LT in CF is controversial.⁴⁴ Liou et al developed a 5-year survivorship model to identify key clinical features of CF and determine the best candidates for LT.⁸² Multivariate logistic regression model assessed 5,820 patients randomly selected from 11,630 patients in the CFFPR in 1993. Models were tested for goodness of fit and were validated for the remaining 5,810 patients. The validated 5-year survivorship model included age, FEV₁ percent predicted, gender, weight-for-age z score, pancreatic sufficiency, diabetes mellitus, *Staphylococcus aureus* infection, *B. cepacia* infection, and annual number of acute pulmonary exacerbations. In 2005, these authors attempted to estimate the survival benefit of LT in CF patients.⁸³ Using data gleaned from the CFFPR and UNOS, 845 LTRs transplanted from 1991 to 2001 for CF, and 12,826 control patients *with CF but without LT* from 1997 were assessed.⁸³ Cox proportional hazards models were used to identify variables that influence post-LT survival. Kaplan–Meier survival curves of transplanted and control patients were stratified by 5-year predicted survival. Factors associated with post-LT hazard of death included youth, colonization or infection with *B. cepacia*, and CF-related arthropathy. Among adults with a 5-year predicted survival of $< 50\%$ and without *B. cepacia* or arthropathy, LT improved survival compared with controls (not transplanted). Importantly, LT never improved survival for pediatric patients. In both children and adults with predicted 5-year survival $> 50\%$, survival was decreased among LTRs. Hence, adult CF patients with *low* 5-year predicted survival and *without B. cepacia* infection should receive priority for LT. The role of LT in children remains controversial.⁸⁴

Thabut et al recently evaluated the survival benefit of LT in *adults* with CF.⁸⁵ UNOS identified 704 adults with CF on a LT waiting list in the United States between 2005 and

2009. Survival times while on the wait list and after LT were modeled by use of a Cox model that incorporated transplantation status as a time-dependent covariate. Evolution in LAS while on the wait list was used as a surrogate for disease severity. The cumulative incidence of LT was 39.3% at 3 months and 64.7% at 12 months, whereas the incidence of death while on the wait list at the same times was 8.5 and 12.9%, respectively. Survival after LT was 96.5% at 3 months, 88.4% at 12 months, and 67.8% at 3 years. LT conferred a 69% reduction in the instantaneous risk of death (51–80%). The interaction between LAS and LT was significant: the higher the LAS, the greater the survival benefit of LT ($p < 0.001$). Hence, LT confers a survival benefit for selected adult patients with CF.

Specific Complications in Cystic Fibrosis Post–Lung Transplantation

Infectious Complications

Because of the high incidence of chronic suppurative pulmonary infections in CF patients, infections post-LT can be serious and life threatening.^{86–88} In the sections that follow, we discuss the most common and serious infectious complications occurring in this patient population.

Sinus Infections

Chronic sinus infection invariably complicates CF^{89,90}; sinus infection with multidrug-resistant (MDR) organisms can persist post-LT.⁹¹ Importantly, colonization/infection of the upper airway may predispose to pulmonary infections.^{91–93} One prospective study in a cohort of 187 CF patients found that upper and lower airway isolates of *Pseudomonas aeruginosa* (PA) were identical in genotype in 23 of 24 PA (+) patients.⁹⁴ Some programs are aggressive in treating sinus disease with surgery.^{89,92} In one series, Holzmann et al reported 37 CF patients who had sinus surgery post-LT; patients in whom sinus surgery was successful had a lower incidence of tracheobronchitis and pneumonia ($p = 0.009$) and a trend toward a lower incidence of bronchiolitis obliterans syndrome (BOS) ($p = 0.23$).⁹⁵ Management of sinus infections with sinus irrigation and inhaled antibiotics is another strategy that has been effective.⁹¹ Randomized, controlled studies are lacking, and optimal approach to sinus disease in CF patients has not been elucidated.²⁵

Pseudomonas aeruginosa

PA is the most common organism colonizing/infecting the airways and sinuses in CF pre-LT, isolated in 56 to 89% of CF patients in pre-LT cultures^{96–100} (Figs. 2 and 3). Post-LT, PA is the most common cause of bronchopulmonary or sinus infections in CF patients.^{101–103} In an early study, 62 LTRs with CF were compared with 52 LTRs without CF.¹⁰¹ Among 50 CF patients surviving at least 15 days post-LT, PA was isolated from the allograft in 44 (88%) [median post-op day (POD) 15] compared with 21 of 52 (40%) non-CF LTRs (median POD 158) ($p < 0.001$).¹⁰¹ Histological evidence for pseudomonal infection was noted in 13 CF patients (compared with 3 non-CF patients) and occurred earlier in CF LTRs (median 10 days) compared with 261 days in the non-CF LTRs, $p > 0.01$. The presence of PA in the airways was associated with inflammation and increased neutrophils in the lung allograft in both CF and non-CF patients. Other investigators evaluated posttransplant microbiology from 120 LTRs (60 had CF).¹⁰² Among the 60 CF

LTRs, 278 postoperative respiratory infections developed, 60% of which were due to PA. Among 60 non-CF LTRs, 154 respiratory infections developed (PA accounted for 38%).¹⁰² Colonization in CF patients post-LT may reflect spread from extrapulmonary reservoirs (especially sinuses).^{91,102,103} The same strain/clone of PA may persist in CF patients pre- and post-LT.^{101,103} Importantly, PA isolates in CF are often MDR.^{104–107} However, panresistant PA in CF LTRs has been associated with a modest reduction in survival in some,¹⁰⁸ but not all,^{109,110} studies. In one two-center study, 103 CF patients post-LT were evaluated (53 from University of Toronto; 50 from Duke University).¹⁰⁸ Overall, 45 patients (44%) harbored panresistant bacteria (i.e., PA [$n = 43$]; *Achromobacter xylosoxidans* [$n = 1$]; *Stenotrophomonas maltophilia* [$n = 1$]). Among resistant and susceptible isolates, survival rates were as follows: 1 year, 88.6 and 96.6%, respectively; 3 years, 63.2 and 90.7%; 5 years, 58.3 and 85.6%. Although survival was reduced in CF patients with panresistant bacteria compared with patients with susceptible organisms, the authors¹⁰⁸ did not believe that panresistance was a contraindication to LT. In a study from Australia, 30 of 54 CF LTRs harbored a panresistant organism pre-LT (28 were PA).¹⁰⁹ Overall survival in the panresistant group was similar to those with susceptible organisms. In a 5-year predicted survival model based on analysis of 845 CF LTRs, infection with PA was *not* a predictor of outcome.⁸³

Treatment of pseudomonal infections in CF patients may be difficult, particularly in MDR strains. Some centers employ perioperative antibiotics at the time of LT using synergy testing (i.e., Multiple Combination Bactericidal Testing or MCBT) to treat MDR-PA,^{104,111} but the value of the practice has not been proven. In one retrospective study from the United Kingdom, CF patients who received LT from 2000 to 2010 received either MCBT ($n = 50$) or conventional antimicrobial therapy ($n = 79$).¹⁰⁴ The incidence of post-LT septicemia was lower with MCBT (4%) versus conventional therapy (16.5%, $p < 0.05$); furthermore, PA was recovered from the post-LT pleural fluid in one patient (2%) in the MCBT group compared with 6.3% in the conventional group ($p = 0.25$). All-cause mortality rates were similar at 30 days (10% MCBT; 6.3% conventional) and at 1 year (22% in MCBT group, 19% in conventional) (NS). In another study, Aaron et al compared the efficacy of MCBT versus conventional therapy as therapy for acute exacerbations of CF in nontransplant patients.¹¹² Clinical and microbiological outcomes were similar between groups. Additional studies are required to assess the value of MCBT in CF patients with MDR or panresistant organisms. Posttransplant, many centers employ inhaled anti-pseudomonal antibiotics (particularly tobramycin or colistin),¹¹³ but controlled randomized trials are lacking.

Interestingly, airway colonization with PA has been associated with an increased risk of chronic lung allograft rejection, manifest as BOS syndrome,¹¹⁴ especially in CF patients.¹¹⁵

Other Bacteria

Over the past two decades, the prevalence of *S. aureus* (both methicillin resistant and methicillin susceptible), *S. maltophilia*,^{116,117} and *Alcaligenes xylosoxidans* has increased in CF patients.^{98,99} These pathogens will not be further discussed here.

Burkholderia cepacia Complex—*B. cepacia* complex (Bcc) comprises a subset of *Burkholderia* species within the genus *Burkholderia*.¹¹⁸ These nonfermenting gram-negative rods infect 2 to 8% of CF patients prior to LT.^{118,119} Importantly, following LT, Bcc usually persists among patients colonized pre-LT.^{120,121} Several distinct species (genomovars) of Bcc have been recognized.^{118,122} Clinical infections in CF patients and epidemics are largely attributed (> 80%) to two species: *B. cenocepacia* (genomovar III)^{122–125} and *B. multivorans* (genomovar II),^{118,125} but other species may cause clinical disease. Different Bcc species vary in virulence, impact on clinical course, and prognosis.^{121,126,127} Mortality is higher among CF patients infected with *B. cenocepacia* (compared with other species),^{121,128} whereas *B. multivorans*-infected patients displayed lower mortality rates compared with *B. cenocepacia* or other species.¹²⁹

The clinical course and prognosis of CF patients infected with Bcc is variable, but numerous studies cited more rapid decline in lung function and heightened mortality among Bcc-infected patients.^{118,126,127,130–137} Pretransplant colonization or infection with *Burkholderia* spp. was associated with increased mortality post-LT in several studies.^{120,121,128,137–143} In one early retrospective study of 53 CF patients undergoing LT in Toronto between 1988 and 1996, isolation of *B. cepacia* pretransplant was associated with increased mortality [15/28 (54%) died compared with 4 of 25 (16%) deaths among *B. cepacia* (–) patients].¹²⁰ Importantly, Bcc persisted in 25/28 patients colonized pre-LT. *B. cepacia* was responsible for 14 deaths; 9 deaths occurred in the first 3 months post-LT. One-year survival was 67% in *B. cepacia* (+) patients compared with 92% for *B. cepacia* (–) patients.¹²⁰ In the Toronto cohort of 124 CF patients receiving LT between 1983 and 2003, 10-year survival rates were 52 and 15%, respectively, for noncolonized and Bcc-colonized patients.¹⁴⁴ In a retrospective review of 121 CF patients receiving LT at the University of North Carolina (UNC), 21 patients were infected/colonized with Bcc pre-LT. Mortality in the first 6 months post-LT was 33% in the Bcc infected/colonized patients compared with 12% in noninfected patients ($p = 0.01$).¹²⁸ One-, 3-, and 5-year survival rates were worse in the Bcc-infected cohort. A subsequent report from UNC cited actuarial survival rates at 1 and 5 years of 60 and 36% among Bcc-colonized patients ($n = 22$) compared with 81 and 59% in noncolonized patients ($n = 99$).²³ In 2008, these investigators reported 75 CF patients who had LT between 1992 and 2002 at UNC; 16 had Bcc isolated pre-LT (7 had *B. cenocepacia*).¹²¹ Of 16 Bcc-colonized patients, 14 (87.5%) remained colonized post-LT. One- and 3-year survival rates post-LT were as follows: 92 and 76% for noninfected patients; 29 and 29% for *B. cenocepacia*-infected patients; 89 and 67% for Bcc species other than *B. cenocepacia*.¹²¹ Antimicrobial susceptibility patterns were not helpful in predicting survival post-LT. Investigators from Newcastle, United Kingdom, reported 216 CF patients who underwent LT; 22 had preoperative Bcc infection (12 due to *B. cenocepacia*).¹³⁹ Nine *B. cenocepacia*-infected recipients died within the first year; Bcc sepsis was the cause of death in 8 patients.¹³⁹ Other Bcc species/ genomovars had significantly better outcomes,¹³⁹ mirroring the experience of others.^{121,126,127} French investigators reported 247 CF patients who had LT in France from 1990 to 2006; 22 were infected with Bcc.¹⁴⁵ Early (3-month) mortality was higher in the Bcc group (15%) compared with 5% mortality in the non-Bcc group ($p < 0.05$). Mortality was higher in patients infected with *B. cenocepacia* ($n = 8$) compared with other Bcc strains ($n = 14$). Six of eight patients with *B. cenocepacia* died; three deaths were

directly linked to *B. cenocepacia* infection in the postoperative period. These data support other studies suggesting heightened virulence and mortality associated with *B. cenocepacia* (compared with other species).^{121,128} Murray et al reviewed 88 Bcc-infected CF patients and 430 noninfected CF patients who had LT at 23 transplant centers in the United States between 1997 and 2006.¹²⁹ Survival rates (1 and 3 years) and HRs differed according to infection and Bcc species. Post-LT survival was similar between *B. multivorans*-infected patients and uninfected patients (HR, 0.66; $p = 0.34$). However, patients infected with nonepidemic strains of *B. cenocepacia* had higher mortality than uninfected recipients (HR, 2.52; $p = 0.04$) or *B. multivorans*-infected patients (HR, 4.39; $p = 0.04$). Mortality was also higher among recipients infected with *B. gladioli* compared with uninfected patients (HR, 2.23, $p > 0.04$). These data support previous studies that different Bcc species vary in virulence, impact on clinical course, and prognosis post-LT. Currently, most centers consider infection/colonization with *Burkholderia cenocepacia* to be a contraindication to LT.^{121,139} However, the role of LT in CF patients colonized/infected with other Bcc species remains controversial.^{118,121,128}

Unfortunately, antimicrobial therapy for *B. cenocepacia* and many strains of Bcc is usually ineffective,^{119,146} because most strains are MDR.^{147–150} All strains are resistant to polymyxin and colistin (this is a hallmark of Bcc).^{147,148} Combinations of antimicrobials^{112,150} and synergy testing¹⁴⁹ have been tried in some centers. In a recent study of CF patients colonized with Bcc, treatment with inhaled aztreonam for 26 weeks was no more effective than placebo in any clinical endpoint.¹⁵¹

Different species within Bcc differ in virulence, persistence, and transmissibility.^{127,152–155} The prevalence of Bcc among Bcc patients is variable over countries/regions, and changes over time.^{118,156} Prevalence rates in the United States,^{119,157} Canada,¹²⁷ United Kingdom, and Europe^{118,124,158} range from 1 to 8%. Much higher rates were cited in the 1980s (up to 18–23%),^{123,156,159} but the prevalence of Bcc declined dramatically with improved infection control measures.¹⁵⁷ Cohorting (segregating) patients dramatically curtails transmission among CF patients, and has become the standard of care.^{157–161} Ongoing transmission of Bcc has been noted in clinics failing to segregate Bcc-infected patients.^{157,162}

Invasive Fungal Infections

Aspergillus Species

Fungal infections (principally from the genus *Aspergillus*) may complicate LT in both CF and non-CF patients^{96,163–173} (Fig. 4). Colonization/infection with *Aspergillus* is common in CF patients prior to LT (19–69%).^{96,164–166,173–176} Colonization is more common in older patients and undoubtedly is favored by selection pressure from use of broad-spectrum antibiotics.¹⁷³ The spectrum of disease associated with *Aspergillus* among CF patients is broad, and includes asymptomatic colonization, allergic bronchopulmonary aspergillosis,^{176–179} tracheobronchitis,^{174,180} and invasive aspergillosis.¹⁷³

Among CF LTRs, the incidence of *Aspergillus* infections is 11 to 22.5%,^{96,164–167,174,175} which is two to four times higher than in non-CF LTRs.^{167,181} In one comprehensive review of LTRs (all indications), the incidence of aspergillosis was 6.2%.¹⁶⁷ In survey of 15

transplant centers in the United States from 2001 to 2006, one-year cumulative incidence of invasive aspergillosis was 3.8% among LTRs (all indications).¹⁸¹ The heightened incidence of *Aspergillus* infections among CF LTRs undoubtedly reflects high colonization rates prior to LT. In a review from Toronto, 65 of 93 (69%) of CF patients receiving LT from 2006 to 2010 were colonized with *Aspergillus* spp. prior to LT.¹⁷⁵ Invasive aspergillosis (IA) developed in 20 of 93 (22.5%) post-LT. Median time to IA was 42 days post-LT. Independent risk factors for IA included (+) intraoperative *Aspergillus* culture of bronchoalveolar lavage (BAL) fluid from the native lung at the time of LT (odds ratio [OR], 4.36) and treatment for acute rejection within 90 days of LT (OR, 3.53). Other reported risk factors for fungal infections post-LT (all indications) include pre-LT colonization^{165,182,183}; colonization with *Aspergillus* within the first 6 months post-LT^{168,175,184}; complicated postoperative course^{87,175}; primary graft dysfunction¹⁷⁵; treatment for acute allograft rejection within 90 days of LT¹⁷⁵; prior respiratory viral infection¹⁶⁵; cytomegalovirus (CMV) infection¹⁸³; single-lung transplant¹⁸⁵; hypogammaglobulinemia¹⁸⁶; renal failure⁸⁷; and BOS.⁸⁷

Airway colonization/infection with *Aspergillus* spp. among LTRs is facilitated by direct exposure to the environment, impaired mucociliary clearance of the denervated lung graft, vulnerable bronchial anastomosis (particularly if ischemic injury had occurred), immunosuppression, and donor-transmitted infections.^{182,187,188} *Aspergillus fumigatus* is responsible for more than 85% of cases of IA among LTRs, but other species (e.g., *A. flavus*, *A. niger*, and *A. terreus*) are capable of causing disease.^{173,182}

Early post-LT (~ days 20–60), *Aspergillus* infections may involve the anastomotic site(s).^{164,167,174,189,190} Cough, stridor/wheeze, dyspnea, or fever may be present, but patients may be asymptomatic (infections are detected by surveillance bronchoscopy).¹⁸² Bronchoscopy may demonstrate ulcerations, granulation tissue, stenosis, areas of necrosis, and pseudomembranes.¹⁸⁹ Complications include bronchostenosis, dehiscence, and bleeding.¹⁹¹ Aggressive medical therapy, including debridement as necessary, is usually curative.^{164,174,189} However, mortality rate associated with *Aspergillus* tracheobronchitis or anastomotic infection is approximately 20%.¹⁸² In the absence of therapy, progression to pulmonary IA may occur.¹⁹² Invasive pulmonary aspergillosis (IPA) (i.e., invasion of lung parenchyma) typically occurs later post-LT (often > 1 year) or in patients with allograft rejection requiring intensive immunosuppression.^{182,193} The diagnosis of IPA may be difficult.^{168,194} Chest computed tomographic (CT) scans may demonstrate nonspecific findings of consolidation or ground glass opacities; focal nodules or cavities (cardinal findings in neutropenic patients with IPA) are usually *not* present in solid organ transplant recipients SOTRs with IPA.¹⁹⁵ Distinguishing colonization from infection may be difficult.^{168,182,196,197} Bronchoscopy with BAL or trans-bronchial biopsies is insensitive to diagnose IPA.¹⁶⁸ Serum galactomannan assays are insensitive (30%) to diagnose IPA among LTRs¹⁹⁶; improved results (sensitivity 60%, specificity 98% for IA) were cited using platelia enzyme immunoassay for galactomannan antigen in BAL fluid.¹⁹⁷ *A. fumigatus* polymerase chain reaction in BAL fluid in LTRs was promising (sensitivity and specificity of 100 and 88%, respectively).¹⁹⁸ Disseminated aspergillosis has been reported among LTRs,¹⁶⁷ but is rare.¹⁸²

Mycetomas may occur in CF patients pre-LT (Fig. 5), and may increase mortality post-LT.¹⁹⁹ In one study, LT was performed in nine patients with mycetomas (none had CF). All received medical therapy before and post-LT. Four patients died within the 1st month post-LT; two others died at 17 and 14 months.¹⁹⁹ Some, but not all, centers consider mycetomas a contraindication to LT.

Treatment of invasive aspergillosis in CF LTRs may be complex, owing to variable pharmacokinetic/pharmacodynamic properties, gastrointestinal absorption, and concomitant medications.^{200,201} Early and aggressive therapy is mandatory.^{202,203} For localized anastomotic fungal infections, medical antifungal therapy, coupled with debridement, is usually curative.^{164,169,174,182} However, for IA, mortality is high (> 50% in some studies).^{163,167,171,204} Voriconazole is the drug of choice for IA,²⁰⁵ either alone or combined with other agents.^{204,206} Voriconazole has been associated with improved outcomes in severely immunosuppressed patients,^{202,205} and is recommended as primary therapy in most guidelines, including the Infectious Disease Society of America.²⁰⁷ Duration of therapy and the role of combination therapy are important unanswered questions.^{202,208} Furthermore, the role of therapeutic drug monitoring for azoles for prophylaxis or treatment regimens in adults is controversial.^{209–211} Liposomal forms of amphotericin B (AmB) are considered as second-line or salvage therapy.²⁰⁷ Caspofungin (an echinocandin) is approved for salvage therapy of IA²¹² but not as primary therapy.²¹³ Posaconazole has been used as salvage therapy for IA, with acceptable results,²¹⁴ but its role has primarily been as prophylactic therapy for specific high-risk populations.^{215,216} Finally, combination therapy with voriconazole, lipid forms of AmB, or caspofungin has been tried with anecdotal successes^{206,217}; however, advantages over mono-therapy have not clearly been established. In one prospective study, 40 SOTRs with IA were treated with caspofungin *plus* voriconazole; results were compared with 47 historical controls treated with liposomal AmB.²⁰⁶ Survival at 90 days was 67.5% (27/40) with combination therapy and 51% (24/47) in the control group (HR, 0.58; $p = 0.117$). However, in SOTRs with renal failure (adjusted HR, 0.32; $p = 0.022$), and in those with *A. fumigatus* infection (adjusted HR, 0.37; $p = 0.019$), combination therapy was independently associated with an improved 90-day survival in multivariate analysis.

In addition to morbidity and mortality associated with invasive *Aspergillus* infections, airway colonization with *Aspergillus* among LTRs (all diagnoses) has been associated with BOS and BOS-related mortality by Cox regression analyses.²¹⁸ *Aspergillus* colonization typically preceded the development of BOS by a median of 261 days (95% confidence interval [CI], 87–520). In a recent two-center study comprising 780 LTRs, BAL colonization with small (but not large) conidia *Aspergillus* spp. was a risk factor for BOS ($p = 0.002$) and was also associated with risk of death ($p = 0.03$).²¹⁹

Given the high mortality and morbidity associated with *Aspergillus* infections, most centers administer antifungal prophylaxis^{188,220–222} following LT (typically with an azole (voriconazole or itraconazole)^{184,187,223} and/or inhaled AmB (deoxycholate or liposomal).^{170,222,224–229} Some centers only administer “targeted” therapy to “high-risk” patients or LTRs with (+) fungal cultures.²³⁰ The optimal strategy, agent, or agents for prophylaxis and *length of therapy* post-LT have not been elucidated,^{187,188,221,222} as

multicenter, randomized studies have not been done. In one retrospective study in high-risk LTRs at high risk for IA (i.e., pre- or posttransplant colonization with *Aspergillus* colonization (except *A. niger*), universal prophylaxis with voriconazole ($n = 65$) was superior to targeted prophylaxis ($n = 30$) with itraconazole +/- inhaled AmB.¹⁸⁴ Rates of IA at 1 year were 1.5% among LTRs receiving voriconazole prophylaxis as compared with 23% in the “targeted prophylaxis” cohort ($p = 0.001$). Another retrospective study examined 67 consecutive LTRs who received prophylaxis with inhaled AmB plus either itraconazole ($n = 32$) or voriconazole ($n = 37$).²²⁷ The incidence of IA was no different between groups, but hepatotoxicity occurred in 12 patients treated with voriconazole compared with no patients receiving itraconazole ($p < 0.001$). Investigators from the Cleveland Clinic cited a lower incidence of IA among LTRs following institution of routine *Aspergillus* prophylaxis with itraconazole or inhaled Am B (4.9%) compared with untreated controls (18.2%, $p < 0.05$).¹⁷⁰ Given the limitations of existing studies, the need for prophylaxis and optimal therapy post-LT remains controversial.^{187,188,221,222} A survey of adult lung transplant centers worldwide in 2009 to 2010 noted that 58.6% of centers used universal antifungal prophylaxis, mostly with voriconazole (alone or combined with inhaled AmB) for 6 months; after 6 months, 51% stopped prophylaxis.²²¹ Intolerance to voriconazole was the main reason for switching to alternative agents. In 2013, the American Society of Transplantation Infectious Diseases Community of Practice recommended antifungal prophylaxis for SOTRs with *Aspergillus* colonization pretransplant or within 12 months post-LT and additionally for recipients with specific risk factors such as acute allograft rejection, augmented immunosuppression, hypogammaglobulinemia, or receipt of antithymocyte globulin.²³¹ Drugs such as inhaled AmB or oral azoles were recommended (itraconazole, voriconazole). We endorse antifungal prophylaxis in all LTRs for at least for the first 6 to 12 months. Our practice is to initiate voriconazole or posaconazole and inhaled AmB during the initial hospitalization for LT, followed by monotherapy with oral voriconazole or posaconazole for a minimum of 6 months. Enthusiasm for chronic use of voriconazole should be tempered by recent studies showing that high cumulative exposure to voriconazole increases the risk of cutaneous squamous cell carcinomas in LTRs^{232–234}; older age and extent of sun exposure further increased the risk.^{232,233}

Fungi/Molds Other than *Aspergillus* spp

Candida spp. may infect the bronchial anastomosis,^{163,182,188,235,236} but invasive pulmonary or disseminated candidiasis is exceedingly rare among LTRs.¹⁸⁸ Serious infections due to Zygomycoses (e.g., *Rhizopus*, *Mucor*, *Absidia*, and *Cunninghamella*),^{237–240} *Fusarium* spp.,^{241,242} *Scedosporium*,^{243–251} and other molds^{194,238,239,252} may complicate LT (all indications). Given the rarity of these disorders, these will not be further addressed here.

Mycobacterial Infections

Tuberculosis (i.e., infection due to *M. tuberculosis*) may occur in immunosuppressed patients and organ transplant recipients,^{253–260} but is rare in CF patients and will not be further addressed here.

Nontuberculous Mycobacteria

In contrast to the low incidence of *M. tuberculosis* in CF patients, nontuberculous mycobacteria (NTM) colonize or infect approximately 15% of adult CF patients prior to LT^{261–268} and may cause invasive clinical infections in CF patients *post-LT*.^{260,269–272} The most common species of NTM isolated in CF patients (pre-LT) is *Mycobacterium avium* complex (MAC), accounting for approximately 45 to 70% of NTM isolates,^{262,268} followed by *M. abscessus* (16–52%),^{262,267–269,273,274} *M. kansasii*,^{263,273,275} *M. fortuitum*,^{263,273,275–277} *M. simiae*,²⁶⁶ *M. haemophilum*,²⁵⁵ and other species.^{255,270} Post-LT, *M. abscessus* has been the predominant NTM responsible for clinical infections.^{269,271,278,279} Clinical manifestations of NTM infection (in CF or non-CF patients) are protean and include pulmonary involvement,^{255,269} empyema,²⁷⁸ localized or disseminated skin/soft tissue infections (SSTI), and^{255,269,280–282} intestinal involvement.²⁸³ Distinguishing colonization with NTM from infection may be difficult; however, multiple positive cultures,²⁸⁴ positive BAL,^{284,285} or nodular or cavitary infiltrates on chest CT scan^{286,287} confirm infection. Clinical features and diagnostic as well as therapeutic approach are elegantly described in article titled “Nontuberculous Mycobacteria in Cystic Fibrosis and Non-Cystic Fibrosis Bronchiectasis” by Drs. Park and Olivier in this issue.

Invasive NTM infections (localized or disseminated) occur in 0.5 to 3.4% of CF patients *post-LT*.^{260,269–271} Early case reports in LTRs in non-CF patients cited infections due to *M. chelonae*²⁸⁸ and *M. fortuitum*²⁸⁹ respectively; subsequent reports (in both CF and non-CF patients) noted that *M. abscessus* was the most common cause of NTM infections *post-LT*.^{269,271,290,291} Some infections were fulminant.^{278,279,282,292} In 1999, a retrospective review of 261 lung and heart–lung transplant recipients (all indications) from Australia detected 25 cases of NTM over 12 years; 19 had extrapulmonary involvement (76%).²⁵⁵ Mean time to diagnosis from LT was 677 days. With therapy, 6 of 6 cutaneous lesions resolved completely and 11 of 16 (69%) pulmonary infections improved. No deaths were attributable to NTM. In another retrospective review of LTRs (all indications), NTM was isolated from 6 of 210 LTRs (2.8%).²⁷⁰ Five of 6 were treated, but only one patient with NTM developed clinical infection (*M. chelonae*). In 2004, Doucette and Fishman reported a case of disseminated MAC in a LTR and identified a total of 22 previously published cases of NTM infections among LTRs.²⁸⁰ The median time to onset of infection was 14.8 months. Knoll et al retrospectively reviewed 237 consecutive LTRs (all indications) between 1990 and 2005 at a single center; NTM were isolated from 53 patients (22.4%) after LT over a median of 25.2 months of follow-up.²⁹³ However, only two patients met criteria for NTM pulmonary disease and required treatment (for MAC). Four patients developed SSTI; three caused by *M. abscessus* and one caused by *M. chelonae*. In three of these patients, the infections persisted requiring chronic suppressive therapy; one died from progressive disseminated disease. Forty-seven patients (89%) met microbiologic, but not radiographic, criteria for pulmonary infection and were not treated; colonization was transient in these patients. Median survival after LT was not different between patients with transient colonization who were not treated and those who never had NTM isolated. We retrospectively reviewed 201 LTRs (all indications) receiving LT at UCLA from 2000 to 2006.²⁷² NTM were isolated from 36 patients (18%), but clinical infection was documented

in only 9 (4.5%); the remaining 27 (13.5%) were considered “colonized.” Single-lung transplant was a significant risk factor for NTM infection (colonization or infection) (HR, 2.25; $p = 0.02$). Further, NTM colonization was a risk factor for NTM disease (HR, 8.39; $p = 0.003$). NTM infection significantly increased the risk of death after LT (HR, 2.61; $p = 0.001$). Interestingly, in multivariate models, both NTM colonization and infection were risk factors for BOS.²⁷²

Data evaluating NTM infections in CF LTRs are limited. Numerous anecdotal case reports and small series in CF LTRs have been published.^{96,282,290,294} Investigators from the UNC reported 146 CF patients who underwent LT at UNC between January 1990 and May 2003 and 31 CF patients waiting for LT in May 2003 at that institution.²⁷¹ The prevalence rates of NTM isolated from respiratory cultures were 19.7% among CF patients *awaiting* LT and 13.7% among CF LTRs.²⁷¹ However, the prevalence of *invasive* NTM disease post-LT was low (3.4%), and was predicted most strongly by pretransplant NTM isolation ($p = 0.001$; OR, 6.13). This association was restricted to *M. abscessus* ($p = 0.005$; OR, 7.45). While NTM disease caused significant morbidity in a small number of patients post-LT, treatment was usually efficacious and post-LT survival was not affected. The authors did not believe that pre-LT isolation of NTM should preclude patients from LT. Several studies suggest that *M. abscessus* has heightened virulence and higher rates of transmissibility compared with other NTM species.^{269,271,290,293} Swedish investigators reported four CF patients with *M. abscessus* pulmonary infections who underwent LT.²⁹⁰ Despite antimicrobial therapy, three patients developed skin infection and abscesses. However, at follow-up after 1, 3, 5, and 7 years, respectively, no patient had evidence of *M. abscessus* infection. In an international survey of approximately 5,200 LTRs (all indications), infections due to *M. abscessus* were identified in only 17 patients (0.33%).²⁶⁹ Median time to diagnosis after LT was 18.5 months (range, 1–111 months). Sites of infection included lung ($n = 12$), skin/soft tissue ($n = 3$), and both skin/soft tissue and lung ($n = 2$).²⁶⁹ Sixteen patients were treated with prolonged combination antimicrobial therapy +/- surgical debridement, 2 patients died, and 10 were cured. Optimal therapy for NTM infections among LTRs has not been clarified. Therapy may be difficult, due to the need for concomitant immunosuppression, and many strains are MDR.²⁹⁵ For clinical infections, prolonged, multiagent antimicrobial therapy is usually required²⁶³ (+/- surgical debridement for refractory disease).²⁶⁹ Aerosolized antibiotics (particularly aminoglycosides) have been used in some cases of infections caused by *M. abscessus*, with anecdotal successes.²⁹⁶

Most transplant centers do not consider pre-LT colonization with NTM to contraindicate LT, provided the infection is controlled. However, to determine which patients are candidates for LT, it is needed to carefully consider the extent and control of infection. As has been discussed, *M. abscessus* likely has higher rates of transmissibility and virulence compared with other NTM species. The risk of recurrent or persistent infection with *M. abscessus* may be high, even with aggressive antimicrobial therapy and minimization of immunosuppression.

The role of transmission of NTM among colonized CF patients has not been well studied.^{297,298} Traditionally, NTM is acquired from environmental sources, and person-to-person transmission is exceptionally rare.²⁹⁹ While no transmission of *M. abscessus* was

found among 214 CF patients (including five colonized patients) in one CF clinic,³⁰⁰ intraclinic transmission of *M. abscessus ss massiliense* (five cases) has been documented; the index case died of disseminated infection following LT.²⁹² All five isolates were indistinguishable by pulsed field gel electrophoresis analysis and genomic testing. This was the first report of *confirmed* person-to-person transmission of NTM. Recently, genome sequence analysis from outbreaks of infections caused by *M. abscessus ss massiliense* in CF centers in the United Kingdom,³⁰¹ Brazil,³⁰² and the United States^{292,303} strongly support patient-to-patient transmission in those clusters.

Cytomegalovirus and Other Human Herpes Viruses

CMV and other herpetic viruses (e.g., Epstein–Barr virus [EBV], varicella zoster virus,^{304,305} herpes simplex virus-1 and -2,³⁰⁴ human herpes virus-6 and -7,³⁰⁶ and community-acquired respiratory viruses) may complicate LT³⁰⁷ but are no more common in CF LTRs compared with other non-CF LTRs and will not be further discussed here.

Noninfectious Complications Post-LT in Cystic Fibrosis Patients

Endocrine Complications

CF-related diabetes mellitus (CFRD) occurs in up to 50% of adults with CF and has correlated with worse pulmonary function and higher mortality.^{308–310} A review of 872 CF patients from Minnesota from 1992 to 2008 cited a prevalence of CFRD in 2% of children, 19% of adolescents, and 40 to 50% of adults.³⁰⁹ Importantly, aggressive treatment³¹¹ has resulted in marked decline in mortality due to CFRD over the past two decades.³⁰⁹ Post-LT, the prevalence of diabetes mellitus (DM) increases (49–77%),^{138,312,313} in part due to concomitant use of corticosteroids and immunosuppressive therapy (particularly calcineurin inhibitors).³¹⁴ In a study of 77 CF LTRs from Toronto, survival was similar between patients with or without DM.³¹² Swiss investigators evaluated 100 CF patients receiving LTs at a single center; 62 had DM pre-LT.³¹³ Interestingly, 1- and 5-year survival rates were higher in LTRs with DM (89 and 71%, respectively) compared with those without DM (71 and 51%, respectively). Furthermore, DM did not impact the development of BOS.

Osteoporosis and osteopenia are nearly invariably present in adult CF patients referred for LT^{315–317}; low pulmonary function, poor nutritional status, low BMI, and vitamin D deficiency are risk factors.^{318–320} Post-LT, accelerated bone loss occurs^{317,321} and pathological fractures and osteonecrosis may occur.^{315,316,322} Nutritional and vitamin supplementations and bisphosphonates are critical to improve bone mass density in CF patients before and after LT.^{317,320,321,323,324}

Gastrointestinal Complications

Gastrointestinal complications (particularly gastroesophageal reflux and intestinal dysmotility) are common in CF^{325–328} and may worsen after LT.^{329–332} Distal intestinal obstruction syndrome³³³ (Fig. 6) may occur in the early postoperative period^{329,334} and may recur. Hepatobiliary disease (e.g., cholestasis, cholelithiasis, common bile duct stenosis, cirrhosis) may complicate CF, and contributes to mortality.^{2,335–337} *C. difficile* colitis is a rare but potentially serious complication following LT.^{338–342} In one series of patients with

CF LTRs, fulminant pseudomembranous colitis developed in four; two died despite urgent colectomy.³⁴³ Malnutrition is an important risk factor for poor outcomes post-LT^{344–346}; pancreatic enzyme supplements and supplemental fat-soluble vitamins are mandatory pre- and post-LT.

Malignancy

Chronic use of immunosuppressive therapy post-LT increases the risk of malignancies (particularly posttransplant lymphoproliferative disorder [PTLD] secondary to EBV).^{347–349} In one series, 5 of 112 EBV seronegative CF patients developed PTLD post-LT.³⁵⁰ The risk of malignancy (particularly neoplasms of the digestive tract) is increased in CF patients.^{351–354} A 20-year survey of more than 40,000 CF patients in the United States from 1990 to 2009 was recently published.³⁵³ In 344,115 patient-years of observation of nontransplanted CF patients, the *overall* cancer risk was similar to background risk. However, the risk of *specific* cancers was higher than expected at the following sites: digestive tract (esophagogastric, biliary tract, small bowel, colon) (OR, 3.5); testicular cancer (OR, 1.7); and lymphoid leukemia (OR, 2.0) but lower for malignant melanoma (OR, 0.4). In 8,235 patient-years of observation of transplanted CF patients, 26 tumors were observed compared with 9.6 expected (OR, 2.7). The increased risk was particularly high for digestive tract cancers (OR, 17.3), with most cases arising in the bowel. Similarly, a European study of more than 24,500 CF patients from 17 countries found a heightened risk for digestive tract malignancies (OR, 6.4) but no higher rates of other cancers.³⁵⁴

Pharmacokinetics, Drug Absorption, and Clearance

Pharmacokinetics and absorption are altered in CF patients, before and after LT. Bioavailability of calcineurin inhibitors may be lower in CF patients, mandating dose adjustment or the use of concomitant agents (e.g., triazoles) that may increase levels.^{355,356}

Retransplantation

Retransplantation has been performed for LTRs (principally with BOS) in both CF and non-CF patients.^{13,357–359} A retrospective cohort study of 205 patients who underwent lung retransplantation between January 2001 and May 2006 in the United States noted a higher risk of death compared with 5,657 patients undergoing *initial* LT ($n = 5,657$) (HR, 1.3; $p < 0.001$).³⁵⁹ From January 1995 through June 2013, 5.1% (799/15,631) of single LTs and 3.4% (925/27,213) of bilateral LTs (all indications) were retransplants (data from the ISHLT Registry)¹³. Mortality rates of adults undergoing retransplantation (all indications) are much higher than primary (first time) LT. From January 1990 to June 2012, median survival among retransplant recipients was only 2.5 years (compared with median survival of 5.7 years for primary LT).¹³ In light of limited availability of donor lungs, the role of retransplantation remains controversial.

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Fig. 1.

Serial chest radiographs of a 23-year-old man with severe cystic fibrosis lung disease, admitted with a respiratory exacerbation that progressed to respiratory failure requiring intubation and mechanical ventilation (**A**). He progressed to acute respiratory distress syndrome and refractory respiratory failure, necessitating venovenous ECMO support (**B**) ECMO cannula entering right internal jugular vein. He underwent successful bilateral lung transplantation after 24 days of ECMO support. (**C**) Immediate postoperative chest radiograph. ECMO, extracorporeal membrane oxygenation.

Fig. 2. Chest CT of a 44-year-old woman with cystic fibrosis with severe lung disease and chronic *Pseudomonas aeruginosa* infection. The classic findings of bronchiectasis, mucus impaction, and air trapping are present. She later underwent successful lung transplantation.

Fig. 3. Chest CT of a 28-year-old woman with cystic fibrosis and chronic multidrug resistant *Pseudomonas aeruginosa* infection, showing extensive bronchiectasis and nearly complete destruction of the right lung. The left lung remains relatively uninvolved but demonstrates areas of mosaic attenuation representative of air trapping.

Fig. 4.

Contrast-enhanced chest CT of a 19-year-old woman with severe cystic fibrosis (CF) lung disease and invasive pulmonary *Aspergillus fumigatus* infection. She was hospitalized with a severe and ultimately fatal respiratory exacerbation while awaiting transplantation. The images reveal the bronchiectasis, mucus plugging, and air trapping that are typical of CF lung disease, as well as patchy opacities and tree-in-bud nodules that likely reflect radiographic manifestations of her acute exacerbation. Note that the main pulmonary artery (PA) is enlarged, and the patient did have secondary pulmonary hypertension with a PA systolic pressure estimated by echocardiogram above 60 mm Hg.

Fig. 5. Chest CT of a 56-year-old woman with cystic fibrosis that demonstrates multiple mycetomas occupying ectatic airways, most prominently in the left lung.

Fig. 6. Abdominal CT of a 45-year-old woman with cystic fibrosis (CF) who had undergone bilateral lung transplantation 16 years prior. She presented with nausea, vomiting, abdominal pain, and distension and was ultimately diagnosed with distal intestinal obstruction syndrome. The CT shows diffusely dilated small bowel with inspissated material in the distal ileum. Of note, the pancreas is atrophic as is often seen in adult CF patients.

Table 1

ISHLT criteria for consideration of lung transplantation in CF patients

Referral to lung transplant center
•FEV ₁ < 30% of baseline or rapid decline in FEV ₁ , particularly if female
•Exacerbation of pulmonary disease requiring ICU stay
•Increasing frequency of exacerbations requiring antibiotic therapy
•Refractory and/or recurrent pneumothorax
•Recurrent hemoptysis not controlled by embolism
Consider lung transplantation
•Oxygen-dependent respiratory failure
•Hypercapnia
•Pulmonary hypertension

Abbreviations: CF, cystic fibrosis; ICU, intensive care unit; FEV₁, forced expiratory volume in 1 second.

Source: Adapted from International Society for Heart and Lung Transplantation (ISHLT) Guidelines.⁴¹