Title

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

Journal

Seminars in Respiratory and Critical Care Medicine, 36(02)

ISSN

1069-3424

Authors

Lynch, Joseph P
Sayah, David M
Belperio, John A
et al.

Publication Date

2015-04-01

DOI

10.1055/s-0035-1547347

Peer reviewed

Published in final edited form as:

Semin Respir Crit Care Med. 2015 April ; 36(2): 299–320. doi:10.1055/s-0035-1547347.

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

Joseph P. Lynch III, MD[1], **David M. Sayah, MD, PhD**[1], **John A. Belperio, MD**[1], and **S. Sam Weigt, MD**[1]

[1]Division of Pulmonary, Critical Care Medicine, Clinical Immunology and Allergy, Department of Internal Medicine, The David Geffen School of Medicine at UCLA, Los Angeles, California

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]

Address for correspondence: Joseph P. Lynch III, MD, Division of Pulmonary, Critical Care Medicine, Clinical Immunology and Allergy, The David Geffen School of Medicine at UCLA, 10833 Le Conte Avenue, 37-131 CHS, Los Angeles, CA 90095 (jplynch@mednet.ucla.edu).

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 HLTwas 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–renal[40] 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 2006[41] 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 FEV_1 has been the most often used functional variable to predict prognosis. In a sentinel article in 1992, Kerem et al reported that $FEV_1 < 30\%$ in CF patients predicted a 2-year mortality of approximately 50%.[45] In that study, other predictors of a worse prognosis included $paO_2 < 50$; $paCO_2 > 55$ mm Hg; female gender; and age < 18 years.[45] In another single-center study, a cutoff value of FEV_1 of < 30% predicted was not a reliable predictor of high risk of death within 2 years; the annual rate of decline of percent predicted FEV_1 was a better parameter to identify those patients at high risk for death.[47] Similarly, Augarten et al reported that FEV_1 did not predict mortality, whereas *rapid rate of decline* of FEV_1 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 tests[52] 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, FEV_1, 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 FEV_1 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, $FEV_1 \leq 30\%$ predicted (hazards ratio [HR], 3.8), $paCO_2 \geq 50$ 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, $FEV_1 \leq 30\%$ predicted (HR, 6.8), $paCO_2 \geq 50$ mm Hg (HR, 6.9), and use of a nutritional intervention (HR, 2.3) were associated with increased risk. Patients with $FEV_1 > 30\%$ predicted had a higher risk of death only when their $paCO_2$ was ≥ 50 mm Hg (HR, 7.0), while the increased risk of death with $FEV_1 \leq 30\%$ 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 FEV_1 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, FEV_1 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 allocation[69]. 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, FEV_1 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 authors[108] 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 testing[149] 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 dysfunction[175]; treatment for acute allograft rejection within 90 days of LT[175]; prior respiratory viral infection[165]; cytomegalovirus (CMV) infection[183]; single-lung transplant[185]; hypogammaglobulinemia[186]; renal failure[87]; 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 LTRs[196]; 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 IA[212] 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 LFTs 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 fuminant.[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 required[263] (+/− 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 LT[307] 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 treatment[311] 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 syndrome[333] (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.

References

1. Quon BS, Aitken ML. Cystic fibrosis: what to expect now in the early adult years. Paediatr Respir Rev. 2012; 13(4):206–214. [PubMed: 23069117]

2. Corris PA. Lung transplantation for cystic fibrosis and bronchiectasis. Semin Respir Crit Care Med. 2013; 34(3):297–304. [PubMed: 23821505]
3. Reid DW, Blizzard CL, Shugg DM, Flowers C, Cash C, Greville HM. Changes in cystic fibrosis mortality in Australia, 1979–2005. Med J Aust. 2011; 195(7):392–395. [PubMed: 21978346]
4. Simmonds NJ. Ageing in cystic fibrosis and long-term survival. Paediatr Respir Rev. 2013; 14(Suppl 1):6–9. [PubMed: 23497942]
5. Annual Data Report. Cystic Fibrosis Foundation; Bethesda, MD: 2005. Cystic Fibrosis Foundation Patient Registry.
6. Dodge JA, Lewis PA, Stanton M, Wilsher J. Cystic fibrosis mortality and survival in the UK: 1947–2003. Eur Respir J. 2007; 29(3):522–526. [PubMed: 17182652]
7. Adler FR, Aurora P, Barker DH, et al. Lung transplantation for cystic fibrosis. Proc Am Thorac Soc. 2009; 6(8):619–633. [PubMed: 20008865]
8. Kotloff RM, Thabut G. Lung transplantation. Am J Respir Crit Care Med. 2011; 184(2):159–171. [PubMed: 21471083]
9. Vizza CD, Yusen RD, Lynch JP, Fedele F, Alexander Patterson G, Trulock EP. Outcome of patients with cystic fibrosis awaiting lung transplantation. Am J Respir Crit Care Med. 2000; 162(3 Pt 1): 819–825. [PubMed: 10988089]
10. Sharples L, Hathaway T, Dennis C, Caine N, Higenbottam T, Wallwork J. Prognosis of patients with cystic fibrosis awaiting heart and lung transplantation. J Heart Lung Transplant. 1993; 12(4): 669–674. [PubMed: 8369328]
11. Ciriaco P, Egan TM, Cairns EL, Thompson JT, Detterbeck FC, Paradowski LJ. Analysis of cystic fibrosis referrals for lung transplantation. Chest. 1995; 107(5):1323–1327. [PubMed: 7750326]
12. Stanchina ML, Tantisira KG, Aquino SL, Wain JC, Ginns LC. Association of lung perfusion disparity and mortality in patients with cystic fibrosis awaiting lung transplantation. J Heart Lung Transplant. 2002; 21(2):217–225. [PubMed: 11834350]
13. Yusen RD, Edwards LB, Kucheryavaya AY, et al. International Society for Heart and Lung Transplantation. The registry of the International Society for Heart and Lung Transplantation: thirty-first adult lung and heart-lung transplant report—2014; focus theme: retransplantation. J Heart Lung Transplant. 2014; 33(10):1009–1024. [PubMed: 25242125]
14. Lanuza DM, Lefaiver C, Mc Cabe M, Farcas GA, Garrity E Jr. Prospective study of functional status and quality of life before and after lung transplantation. Chest. 2000; 118(1):115–122. [PubMed: 10893368]
15. Durst CL, Horn MV, MacLaughlin EF, Bowman CM, Starnes VA, Woo MS. Psychosocial responses of adolescent cystic fibrosis patients to lung transplantation. Pediatr Transplant. 2001; 5(1):27–31. [PubMed: 11260485]
16. Vermeulen KM, van der Bij W, Erasmus ME, Duiverman EJ, Koëter GH, TenVergert EM. Improved quality of life after lung transplantation in individuals with cystic fibrosis. Pediatr Pulmonol. 2004; 37(5):419–426. [PubMed: 15095325]
17. Kugler C, Strueber M, Tegtbur U, Niedermeyer J, Haverich A. Quality of life 1 year after lung transplantation. Prog Transplant. 2004; 14(4):331–336. [PubMed: 15663018]
18. Yacoub MH, Banner NR, Khaghani A, et al. Heart-lung transplantation for cystic fibrosis and subsequent domino heart transplantation. J Heart Transplant. 1990; 9(5):459–466. discussion 466–467. [PubMed: 2231084]
19. de Leval MR, Smyth R, Whitehead B, et al. Heart and lung transplantation for terminal cystic fibrosis. A 4 1/2-year experience. J Thorac Cardiovasc Surg. 1991; 101(4):633–641. discussion 641–642. [PubMed: 2008101]
20. Vricella LA, Karamichalis JM, Ahmad S, Robbins RC, Whyte RI, Reitz BA. Lung and heart-lung transplantation in patients with end-stage cystic fibrosis: the Stanford experience. Ann Thorac Surg. 2002; 74(1):13–17. discussion 17–18. [PubMed: 12118744]
21. Shennib H, Noirclerc M, Ernst P, et al. The Cystic Fibrosis Transplant Study Group. Double-lung transplantation for cystic fibrosis. Ann Thorac Surg. 1992; 54(1):27–31. discussion 31–32. [PubMed: 1610249]

22. Ganesh JS, Rogers CA, Bonser RS, Banner NR. Steering Group of the UK Cardiothoracic Transplant Audit. Outcome of heart-lung and bilateral sequential lung transplantation for cystic fibrosis: a UK national study. Eur Respir J. 2005; 25(6):964–969. [PubMed: 15929949]
23. Egan TM, Detterbeck FC, Mill MR, et al. Long term results of lung transplantation for cystic fibrosis. Eur J Cardiothorac Surg. 2002; 22(4):602–609. [PubMed: 12297180]
24. Mendeloff EN, Huddleston CB, Mallory GB, et al. Pediatric and adult lung transplantation for cystic fibrosis. J Thorac Cardiovasc Surg. 1998; 115(2):404–413. discussion 413–414. [PubMed: 9475536]
25. Spahr JE, Love RB, Francois M, Radford K, Meyer KC. Lung transplantation for cystic fibrosis: current concepts and one center's experience. J Cyst Fibros. 2007; 6(5):334–350. [PubMed: 17418647]
26. Samano MN, Pêgo-Fernandes PM, Fonseca Ribeiro AK, et al. Lung transplantation in patients with cystic fibrosis. Transplant Proc. 2013; 45(3):1137–1141. [PubMed: 23622646]
27. Diso D, Anile M, Patella M, et al. Lung transplantation for cystic fibrosis: outcome of 101 single-center consecutive patients. Transplant Proc. 2013; 45(1):346–348. [PubMed: 23375321]
28. Venuta F, Diso D, Anile M, et al. Evolving techniques and perspectives in lung transplantation. Transplant Proc. 2005; 37(6):2682–2683. [PubMed: 16182783]
29. Coloni GF, Venuta F, Ciccone AM, et al. Lung transplantation for cystic fibrosis. Transplant Proc. 2004; 36(3):648–650. [PubMed: 15110621]
30. Starnes VA, Barr ML, Cohen RG, et al. Living-donor lobar lung transplantation experience: intermediate results. J Thorac Cardiovasc Surg. 1996; 112(5):1284–1290. discussion 1290–1291. [PubMed: 8911325]
31. Barr ML, Schenkel FA, Cohen RG, et al. Recipient and donor outcomes in living related and unrelated lobar transplantation. Transplant Proc. 1998; 30(5):2261–2263. [PubMed: 9723463]
32. Woo MS, MacLaughlin EF, Horn MV, et al. Living donor lobar lung transplantation: the pediatric experience. Pediatr Transplant. 1998; 2(3):185–190. [PubMed: 10084740]
33. Cohen RG, Barr ML, Schenkel FA, DeMeester TR, Wells WJ, Starnes VA. Living-related donor lobectomy for bilateral lobar transplantation in patients with cystic fibrosis. Ann Thorac Surg. 1994; 57(6):1423–1427. discussion 1428. [PubMed: 8010783]
34. Starnes VA, Bowdish ME, Woo MS, et al. A decade of living lobar lung transplantation: recipient outcomes. J Thorac Cardiovasc Surg. 2004; 127(1):114–122. [PubMed: 14752421]
35. Date H, Aoe M, Sano Y, et al. Improved survival after living-donor lobar lung transplantation. J Thorac Cardiovasc Surg. 2004; 128(6):933–940. [PubMed: 15573079]
36. Mitilian D, Sage E, Puyo P, et al. Foch Lung Transplant Group. Techniques and results of lobar lung transplantations. Eur J Cardiothorac Surg. 2014; 45(2):365–369. discussion 369–370. [PubMed: 23900745]
37. Inci I, Schuurmans MM, Kestenholz P, et al. Long-term outcomes of bilateral lobar lung transplantation. Eur J Cardiothorac Surg. 2013; 43(6):1220–1225. [PubMed: 23091227]
38. Harring TR, Nguyen NT, Liu H, Karpen SJ, Goss JA, O'Mahony CA. Liver transplantation in cystic fibrosis: a report from Baylor College of Medicine and the Texas Children's Hospital. Pediatr Transplant. 2013; 17(3):271–277. [PubMed: 23489441]
39. Van De Wauwer C, Verschuuren EA, Nossent GD, et al. A staged approach for a lung-liver transplant patient using ex vivo reconditioned lungs first followed by an urgent liver transplantation. Transpl Int. 2015; 28(1):129–133. [PubMed: 25070399]
40. Borro JM, Rama P, Rey T, Fernández-Rivera C. Long-term success of combined kidney-lung transplantation in a patient with cystic fibrosis. Arch Bronconeumol. 2013; 49(6):272–274. [PubMed: 23427867]
41. Orens JB, Estenne M, Arcasoy S, et al. Pulmonary Scientific Council of the International Society for Heart and Lung Transplantation. 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(7): 745–755. [PubMed: 16818116]

42. Belkin RA, Henig NR, Singer LG, et al. Risk factors for death of patients with cystic fibrosis awaiting lung transplantation. Am J Respir Crit Care Med. 2006; 173(6):659–666. [PubMed: 16387803]
43. Liou TG, Woo MS, Cahill BC. Lung transplantation for cystic fibrosis. Curr Opin Pulm Med. 2006; 12(6):459–463. [PubMed: 17053498]
44. Hirche TO, Knoop C, Hebestreit H, et al. ECORN-CF Study Group. Practical guidelines: lung transplantation in patients with cystic fibrosis. Pulm Med. 2014; 2014:621342. [PubMed: 24800072]
45. Kerem E, Reisman J, Corey M, Canny GJ, Levison H. Prediction of mortality in patients with cystic fibrosis. N Engl J Med. 1992; 326(18):1187–1191. [PubMed: 1285737]
46. Rosenbluth DB, Wilson K, Ferkol T, Schuster DP. Lung function decline in cystic fibrosis patients and timing for lung transplantation referral. Chest. 2004; 126(2):412–419. [PubMed: 15302726]
47. Milla CE, Warwick WJ. Risk of death in cystic fibrosis patients with severely compromised lung function. Chest. 1998; 113(5):1230–1234. [PubMed: 9596299]
48. Augarten A, Akons H, Aviram M, et al. Prediction of mortality and timing of referral for lung transplantation in cystic fibrosis patients. Pediatr Transplant. 2001; 5(5):339–342. [PubMed: 11560752]
49. Venuta F, Rendina EA, De Giacomo T, et al. Timing and priorities for cystic fibrosis patients candidates to lung transplantation. Eur J Pediatr Surg. 1998; 8(5):274–277. [PubMed: 9825236]
50. Venuta F, Rendina EA, Rocca GD, et al. Pulmonary hemodynamics contribute to indicate priority for lung transplantation in patients with cystic fibrosis. J Thorac Cardiovasc Surg. 2000; 119(4 Pt 1):682–689. [PubMed: 10733756]
51. Hayes D Jr, Tobias JD, Mansour HM, et al. Pulmonary hypertension in cystic fibrosis with advanced lung disease. Am J Respir Crit Care Med. 2014; 190(8):898–905. [PubMed: 25222938]
52. Tuppin MP, Paratz JD, Chang AT, et al. Predictive utility of the 6-minute walk distance on survival in patients awaiting lung transplantation. J Heart Lung Transplant. 2008; 27(7):729–734. [PubMed: 18582801]
53. Mayer-Hamblett N, Rosenfeld M, Emerson J, Goss CH, Aitken ML. Developing cystic fibrosis lung transplant referral criteria using predictors of 2-year mortality. Am J Respir Crit Care Med. 2002; 166(12 Pt 1):1550–1555. [PubMed: 12406843]
54. Ellaffi M, Vinsonneau C, Coste J, et al. One-year outcome after severe pulmonary exacerbation in adults with cystic fibrosis. Am J Respir Crit Care Med. 2005; 171(2):158–164. [PubMed: 15502116]
55. Hayes D Jr, Higgins RS, Kirkby S, et al. Impact of pulmonary hypertension on survival in patients with cystic fibrosis undergoing lung transplantation: an analysis of the UNOS registry. J Cyst Fibros. 2014; 13(4):416–423. [PubMed: 24388063]
56. Flume PA. Pneumothorax in cystic fibrosis. Chest. 2003; 123(1):217–221. [PubMed: 12527625]
57. Smyth RL, Scott JP, McGoldrick JP, Higenbottam TW, Wallwork J. Heart-lung transplantation for pneumothorax in cystic fibrosis. Ann Thorac Surg. 1989; 48(5):744–745. [PubMed: 2818077]
58. Curtis HJ, Bourke SJ, Dark JH, Corris PA. Lung transplantation outcome in cystic fibrosis patients with previous pneumothorax. J Heart Lung Transplant. 2005; 24(7):865–869. [PubMed: 15982615]
59. Detterbeck FC, Egan TM, Mill MR. Lung transplantation after previous thoracic surgical procedures. Ann Thorac Surg. 1995; 60(1):139–143. [PubMed: 7598576]
60. Rolla M, Anile M, Venuta F, et al. Lung transplantation for cystic fibrosis after thoracic surgical procedures. Transplant Proc. 2011; 43(4):1162–1163. [PubMed: 21620078]
61. Dusmet M, Winton TL, Kesten S, Maurer J. Previous intrapleural procedures do not adversely affect lung transplantation. J Heart Lung Transplant. 1996; 15(3):249–254. [PubMed: 8777207]
62. Elizur A, Sweet SC, Huddleston CB, et al. Pre-transplant mechanical ventilation increases short-term morbidity and mortality in pediatric patients with cystic fibrosis. J Heart Lung Transplant. 2007; 26(2):127–131. [PubMed: 17258145]
63. Efrati O, Bylin I, Segal E, et al. Outcome of patients with cystic fibrosis admitted to the intensive care unit: is invasive mechanical ventilation a risk factor for death in patients waiting lung transplantation? Heart Lung. 2010; 39(2):153–159. [PubMed: 20207276]

64. Bartz RR, Love RB, Leverson GE, Will LR, Welter DL, Meyer KC. Pre-transplant mechanical ventilation and outcome in patients with cystic fibrosis. J Heart Lung Transplant. 2003; 22(4):433–438. [PubMed: 12681421]

65. Massard G, Shennib H, Metras D, et al. Double-lung transplantation in mechanically ventilated patients with cystic fibrosis. Ann Thorac Surg. 1993; 55(5):1087–1091. discussion 1091–1092. [PubMed: 8494415]

66. Sood N, Paradowski LJ, Yankaskas JR. Outcomes of intensive care unit care in adults with cystic fibrosis. Am J Respir Crit Care Med. 2001; 163(2):335–338. [PubMed: 11179102]

67. Flume PA, Egan TM, Westerman JH, et al. Lung transplantation for mechanically ventilated patients. J Heart Lung Transplant. 1994; 13(1 Pt 1):15–21. discussion 22–23. [PubMed: 7513185]

68. Mason DP, Thuita L, Nowicki ER, Murthy SC, Pettersson GB, Blackstone EH. Should lung transplantation be performed for patients on mechanical respiratory support? The US experience. J Thorac Cardiovasc Surg. 2010; 139(3):765–773. e1. [PubMed: 19931096]

69. Singer JP, Blanc PD, Hoopes C, et al. The impact of pretransplant mechanical ventilation on short- and long-term survival after lung transplantation. Am J Transplant. 2011; 11(10):2197–2204. [PubMed: 21831157]

70. Lang G, Taghavi S, Aigner C, et al. Primary lung transplantation after bridge with extracorporeal membrane oxygenation: a plea for a shift in our paradigms for indications. Transplantation. 2012; 93(7):729–736. [PubMed: 22415051]

71. Casswell GK, Pilcher DV, Martin RS, et al. Buying time: The use of extracorporeal membrane oxygenation as a bridge to lung transplantation in pediatric patients. Pediatr Transplant. 2013; 17(8):E182–E188. [PubMed: 24164831]

72. Anile M, Diso D, Russo E, et al. Extracorporeal membrane oxygenation as bridge to lung transplantation. Transplant Proc. 2013; 45(7):2621–2623. [PubMed: 24034007]

73. Lafarge M, Mordant P, Thabut G, et al. Experience of extracorporeal membrane oxygenation as a bridge to lung transplantation in France. J Heart Lung Transplant. 2013; 32(9):905–913. [PubMed: 23953818]

74. Toyoda Y, Bhama JK, Shigemura N, et al. Efficacy of extracorporeal membrane oxygenation as a bridge to lung transplantation. J Thorac Cardiovasc Surg. 2013; 145(4):1065–1070. discussion 1070–1071. [PubMed: 23332185]

75. Garcia JP, Kon ZN, Evans C, et al. Ambulatory veno-venous extracorporeal membrane oxygenation: innovation and pitfalls. J Thorac Cardiovasc Surg. 2011; 142(4):755–761. [PubMed: 21924145]

76. Fuehner T, Kuehn C, Hadem J, et al. Extracorporeal membrane oxygenation in awake patients as bridge to lung transplantation. Am J Respir Crit Care Med. 2012; 185(7):763–768. [PubMed: 22268135]

77. Olsson KM, Simon A, Strueber M, et al. Extracorporeal membrane oxygenation in nonintubated patients as bridge to lung transplantation. Am J Transplant. 2010; 10(9):2173–2178. [PubMed: 20636463]

78. Schmidt F, Sasse M, Boehne M, et al. Concept of “awake venovenous extracorporeal membrane oxygenation” in pediatric patients awaiting lung transplantation. Pediatr Transplant. 2013; 17(3): 224–230. [PubMed: 23050564]

79. Hayes D Jr, Kukreja J, Tobias JD, Ballard HO, Hoopes CW. Ambulatory venovenous extracorporeal respiratory support as a bridge for cystic fibrosis patients to emergent lung transplantation. J Cyst Fibros. 2012; 11(1):40–45. [PubMed: 22035707]

80. Hayes D Jr, Galantowicz M, Yates AR, Preston TJ, Mansour HM, McConnell PI. Venovenous ECMO as a bridge to lung transplant and a protective strategy for subsequent primary graft dysfunction. J Artif Organs. 2013; 16(3):382–385. [PubMed: 23508264]

81. Kirkby S, Whitson BA, Wehr AM, Lehman AM, Higgins RS, Hayes D Jr. Survival benefit of induction immunosuppression in cystic fibrosis lung transplant recipients. J Cyst Fibros. 2015; 14(1):104–110. [PubMed: 24948447]

82. Liou TG, Adler FR, Fitzsimmons SC, Cahill BC, Hibbs JR, Marshall BC. Predictive 5-year survivorship model of cystic fibrosis. Am J Epidemiol. 2001; 153(4):345–352. [PubMed: 11207152]

83. Liou TG, Adler FR, Huang D. Use of lung transplantation survival models to refine patient selection in cystic fibrosis. Am J Respir Crit Care Med. 2005; 171(9):1053–1059. [PubMed: 15695493]
84. Kirkby S, Hayes D Jr. Pediatric lung transplantation: indications and outcomes. J Thorac Dis. 2014; 6(8):1024–1031. [PubMed: 25132969]
85. 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; 187(12):1335–1340. [PubMed: 23590274]
86. Lobo LJ, Noone PG. Respiratory infections in patients with cystic fibrosis undergoing lung transplantation. The lancet Respir Med. 2014; 2:73–82. [PubMed: 24461904]
87. Remund KF, Best M, Egan JJ. Infections relevant to lung transplantation. Proc Am Thorac Soc. 2009; 6(1):94–100. [PubMed: 19131534]
88. Dorgan DJ, Hadjiliadis D. Lung transplantation in patients with cystic fibrosis: special focus to infection and comorbidities. Expert Rev Respir Med. 2014; 8(3):315–326. [PubMed: 24655065]
89. Robertson JM, Friedman EM, Rubin BK. Nasal and sinus disease in cystic fibrosis. Paediatr Respir Rev. 2008; 9(3):213–219. [PubMed: 18694713]
90. Rosbe KW, Jones DT, Rahbar R, Lahiri T, Auerbach AD. Endoscopic sinus surgery in cystic fibrosis: do patients benefit from surgery? Int J Pediatr Otorhinolaryngol. 2001; 61(2):113–119. [PubMed: 11589977]
91. Mainz JG, Hentschel J, Schien C, et al. Sinonasal persistence of Pseudomonas aeruginosa after lung transplantation. J Cyst Fibros. 2012; 11(2):158–161. [PubMed: 22133899]
92. Aanæs K. Bacterial sinusitis can be a focus for initial lung colonisation and chronic lung infection in patients with cystic fibrosis. J Cyst Fibros. 2013; 12(Suppl 2):S1–S20. [PubMed: 24064077]
93. Ciofu O, Johansen HK, Aanaes K, et al. P. aeruginosa in the paranasal sinuses and transplanted lungs have similar adaptive mutations as isolates from chronically infected CF lungs. J Cyst Fibros. 2013; 12(6):729–736. [PubMed: 23478131]
94. Mainz JG, Naehrlich L, Schien M, et al. Concordant genotype of upper and lower airways P aeruginosa and S aureus isolates in cystic fibrosis. Thorax. 2009; 64(6):535–540. [PubMed: 19282318]
95. Holzmann D, Speich R, Kaufmann T, et al. Effects of sinus surgery in patients with cystic fibrosis after lung transplantation: a 10-year experience. Transplantation. 2004; 77(1):134–136. [PubMed: 14724449]
96. Flume PA, Egan TM, Paradowski LJ, Detterbeck FC, Thompson JT, Yankaskas JR. Infectious complications of lung transplantation. Impact of cystic fibrosis. Am J Respir Crit Care Med. 1994; 149(6):1601–1607. [PubMed: 7516251]
97. Kanj SS, Tapson V, Davis RD, Madden J, Browning I. Infections in patients with cystic fibrosis following lung transplantation. Chest. 1997; 112(4):924–930. [PubMed: 9377954]
98. Razvi S, Quittell L, Sewall A, Quinton H, Marshall B, Saiman L. Respiratory microbiology of patients with cystic fibrosis in the United States, 1995 to 2005. Chest. 2009; 136(6):1554–1560. [PubMed: 19505987]
99. Millar FA, Simmonds NJ, Hodson ME. Trends in pathogens colonising the respiratory tract of adult patients with cystic fibrosis, 1985–2005. J Cyst Fibros. 2009; 8(6):386–391. [PubMed: 19740710]
100. Li Z, Kosorok MR, Farrell PM, et al. Longitudinal development of mucoid Pseudomonas aeruginosa infection and lung disease progression in children with cystic fibrosis. JAMA. 2005; 293(5):581–588. [PubMed: 15687313]
101. Nunley DR, Grgurich W, Iacono AT, et al. Allograft colonization and infections with pseudomonas in cystic fibrosis lung transplant recipients. Chest. 1998; 113(5):1235–1243. [PubMed: 9596300]
102. Bonvillain RW, Valentine VG, Lombard G, LaPlace S, Dhillon G, Wang G. Post-operative infections in cystic fibrosis and non-cystic fibrosis patients after lung transplantation. J Heart Lung Transplant. 2007; 26(9):890–897. [PubMed: 17845927]

103. Walter S, Gudowius P, Bosshammer J, et al. Epidemiology of chronic Pseudomonas aeruginosa infections in the airways of lung transplant recipients with cystic fibrosis. Thorax. 1997; 52(4): 318–321. [PubMed: 9196512]
104. Haja Mydin H, Corris PA, Nicholson A, et al. Targeted antibiotic prophylaxis for lung transplantation in cystic fibrosis patients colonised with Pseudomonas aeruginosa using multiple combination bactericidal testing. J Transplant. 2012; 2012:135738. [PubMed: 22848792]
105. Pitt TL, Sparrow M, Warner M, Stefanidou M. Survey of resistance of Pseudomonas aeruginosa from UK patients with cystic fibrosis to six commonly prescribed antimicrobial agents. Thorax. 2003; 58(9):794–796. [PubMed: 12947141]
106. Perry JD, Laine L, Hughes S, Nicholson A, Galloway A, Gould FK. Recovery of antimicrobial-resistant Pseudomonas aeruginosa from sputa of cystic fibrosis patients by culture on selective media. J Antimicrob Chemother. 2008; 61(5):1057–1061. [PubMed: 18316821]
107. Dales L, Ferris W, Vandemheen K, Aaron SD. Combination antibiotic susceptibility of biofilm-grown Burkholderia cepacia and Pseudomonas aeruginosa isolated from patients with pulmonary exacerbations of cystic fibrosis. Eur J Clin Microbiol Infect Dis. 2009; 28(10):1275–1279. [PubMed: 19575248]
108. Hadjiliadis D, Steele MP, Chaparro C, et al. Survival of lung transplant patients with cystic fibrosis harboring panresistant bacteria other than Burkholderia cepacia, compared with patients harboring sensitive bacteria. J Heart Lung Transplant. 2007; 26(8):834–838. [PubMed: 17692788]
109. 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 centre. J Hosp Infect. 2004; 56(4):277–282. [PubMed: 15066737]
110. Aris RM, Gilligan PH, Neuringer IP, Gott KK, Rea J, Yankaskas JR. The effects of panresistant bacteria in cystic fibrosis patients on lung transplant outcome. Am J Respir Crit Care Med. 1997; 155(5):1699–1704. [PubMed: 9154879]
111. Lang BJ, Aaron SD, Ferris W, Hebert PC, MacDonald NE. Multiple combination bactericidal antibiotic testing for patients with cystic fibrosis infected with multiresistant strains of Pseudomonas aeruginosa. Am J Respir Crit Care Med. 2000; 162(6):2241–2245. [PubMed: 11112146]
112. Aaron SD, Vandemheen KL, Ferris W, et al. Combination antibiotic susceptibility testing to treat exacerbations of cystic fibrosis associated with multiresistant bacteria: a randomised, double-blind, controlled clinical trial. Lancet. 2005; 366(9484):463–471. [PubMed: 16084254]
113. Suhling H, Rademacher J, Greer M, et al. Inhaled colistin following lung transplantation in colonised cystic fibrosis patients. Eur Respir J. 2013; 42(2):542–544. [PubMed: 23904550]
114. 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(5):771–774. [PubMed: 18337673]
115. Vos R, Vanaudenaerde BM, Geudens N, Dupont LJ, Van Raemdonck DE, Verleden GM. Pseudomonal airway colonisation: risk factor for bronchiolitis obliterans syndrome after lung transplantation? Eur Respir J. 2008; 31(5):1037–1045. [PubMed: 18256072]
116. Waters V, Atenafu EG, Lu A, Yau Y, Tullis E, Ratjen F. Chronic Stenotrophomonas maltophilia infection and mortality or lung transplantation in cystic fibrosis patients. J Cyst Fibros. 2013; 12(5):482–486. [PubMed: 23294530]
117. Stanojevic S, Ratjen F, Stephens D, et al. Factors influencing the acquisition of Stenotrophomonas maltophilia infection in cystic fibrosis patients. J Cyst Fibros. 2013; 12(6): 575–583. [PubMed: 23757360]
118. Lynch JP III. Burkholderia cepacia complex: impact on the cystic fibrosis lung lesion. Semin Respir Crit Care Med. 2009; 30(5):596–610. [PubMed: 19760547]
119. LiPuma JJ. Burkholderia and emerging pathogens in cystic fibrosis. Semin Respir Crit Care Med. 2003; 24(6):681–692. [PubMed: 16088584]
120. 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(1):43–48. [PubMed: 11208624]

121. Alexander BD, Petzold EW, Reller LB, et al. Survival after lung transplantation of cystic fibrosis patients infected with Burkholderia cepacia complex. Am J Transplant. 2008; 8(5):1025–1030. [PubMed: 18318775]

122. Coenye T, Vandamme P, Govan JR, LiPuma JJ. Taxonomy and identification of the Burkholderia cepacia complex. J Clin Microbiol. 2001; 39(10):3427–3436. [PubMed: 11574551]

123. Chen JS, Witzmann KA, Spilker T, Fink RJ, LiPuma JJ. Endemicity and inter-city spread of Burkholderia cepacia genomovar III in cystic fibrosis. J Pediatr. 2001; 139(5):643–649. [PubMed: 11713440]

124. Coenye T, Spilker T, Van Schoor A, LiPuma JJ, Vandamme P. Recovery of Burkholderia cenocepacia strain PHDC from cystic fibrosis patients in Europe. Thorax. 2004; 59(11):952–954. [PubMed: 15516470]

125. Holden MT, Seth-Smith HM, Crossman LC, et al. The genome of Burkholderia cenocepacia J2315, an epidemic pathogen of cystic fibrosis patients. J Bacteriol. 2009; 191(1):261–277. [PubMed: 18931103]

126. Jones AM, Dodd ME, Govan JR, et al. Burkholderia cenocepacia and Burkholderia multivorans: influence on survival in cystic fibrosis. Thorax. 2004; 59(11):948–951. [PubMed: 15516469]

127. Mahenthiralingam E, Vandamme P, Campbell ME, et al. Infection with Burkholderia cepacia complex genomovars in patients with cystic fibrosis: virulent transmissible strains of genomovar III can replace Burkholderia multivorans. Clin Infect Dis. 2001; 33(9):1469–1475. [PubMed: 11588691]

128. Aris RM, Routh JC, LiPuma JJ, Heath DG, Gilligan PH. Lung transplantation for cystic fibrosis patients with Burkholderia cepacia complex. Survival linked to genomovar type. Am J Respir Crit Care Med. 2001; 164(11):2102–2106. [PubMed: 11739142]

129. Murray S, Charbeneau J, Marshall BC, LiPuma JJ. Impact of burkholderia infection on lung transplantation in cystic fibrosis. Am J Respir Crit Care Med. 2008; 178(4):363–371. [PubMed: 18535253]

130. Frangolias DD, Mahenthiralingam E, Rae S, et al. Burkholderia cepacia in cystic fibrosis. Variable disease course. Am J Respir Crit Care Med. 1999; 160(5 Pt 1):1572–1577. [PubMed: 10556123]

131. Manno G, Dalmastri C, Tabacchioni S, et al. Epidemiology and clinical course of Burkholderia cepacia complex infections, particularly those caused by different Burkholderia cenocepacia strains, among patients attending an Italian Cystic Fibrosis Center. J Clin Microbiol. 2004; 42(4): 1491–1497. [PubMed: 15070994]

132. Tablan OC, Martone WJ, Doershuk CF, et al. Colonization of the respiratory tract with Pseudomonas cepacia in cystic fibrosis. Risk factors and outcomes. Chest. 1987; 91(4):527–532. [PubMed: 3829745]

133. Kalish LA, Waltz DA, Dovey M, et al. Impact of Burkholderia dolosa on lung function and survival in cystic fibrosis. Am J Respir Crit Care Med. 2006; 173(4):421–425. [PubMed: 16272450]

134. Ledson MJ, Gallagher MJ, Jackson M, Hart CA, Walshaw MJ. Outcome of Burkholderia cepacia colonisation in an adult cystic fibrosis centre. Thorax. 2002; 57(2):142–145. [PubMed: 11828044]

135. Muhdi K, Edenborough FP, Gumery L, et al. Outcome for patients colonised with Burkholderia cepacia in a Birmingham adult cystic fibrosis clinic and the end of an epidemic. Thorax. 1996; 51(4):374–377. [PubMed: 8733488]

136. Lewin LO, Byard PJ, Davis PB. Effect of Pseudomonas cepacia colonization on survival and pulmonary function of cystic fibrosis patients. J Clin Epidemiol. 1990; 43(2):125–131. [PubMed: 2303842]

137. De Soyza A, Archer L, Wardle J, et al. Pulmonary transplantation for cystic fibrosis: pre-transplant recipient characteristics in patients dying of peri-operative sepsis. J Heart Lung Transplant. 2003; 22(7):764–769. [PubMed: 12873544]

138. Meachery G, De Soyza A, Nicholson A, et al. Outcomes of lung transplantation for cystic fibrosis in a large UK cohort. Thorax. 2008; 63(8):725–731. [PubMed: 18487317]

139. 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(12):1395–1404. [PubMed: 20810293]
140. Snell GI, de Hoyos A, Krajden M, Winton T, Maurer JR. Pseudomonas cepacia in lung transplant recipients with cystic fibrosis. Chest. 1993; 103(2):466–471. [PubMed: 7679347]
141. De Soyza A, McDowell A, Archer L, et al. Burkholderia cepacia complex genomovars and pulmonary transplantation outcomes in patients with cystic fibrosis. Lancet. 2001; 358(9295): 1780–1781. [PubMed: 11734238]
142. Egan JJ, McNeil K, Bookless B, et al. Post-transplantation survival of cystic fibrosis patients infected with Pseudomonas cepacia. Lancet. 1994; 344(8921):552–553. [PubMed: 7520109]
143. Savi D, De Biase RV, Amaddeo A, et al. Burkholderia pyrrocinia in cystic fibrosis lung transplantation: a case report. Transplant Proc. 2014; 46(1):295–297. [PubMed: 24507071]
144. de Perrot M, Chaparro C, McRae K, et al. Twenty-year experience of lung transplantation at a single center: Influence of recipient diagnosis on long-term survival. J Thorac Cardiovasc Surg. 2004; 127(5):1493–1501. [PubMed: 15116013]
145. Boussaud V, Guillemain R, Grenet D, et al. Clinical outcome following lung transplantation in patients with cystic fibrosis colonised with Burkholderia cepacia complex: results from two French centres. Thorax. 2008; 63(8):732–737. [PubMed: 18408050]
146. Aaron SD, Ferris W, Henry DA, Speert DP, Macdonald NE. Multiple combination bactericidal antibiotic testing for patients with cystic fibrosis infected with Burkholderia cepacia. Am J Respir Crit Care Med. 2000; 161(4 Pt 1):1206–1212. [PubMed: 10764313]
147. Zhou J, Chen Y, Tabibi S, Alba L, Garber E, Saiman L. Antimicrobial susceptibility and synergy studies of Burkholderia cepacia complex isolated from patients with cystic fibrosis. Antimicrob Agents Chemother. 2007; 51(3):1085–1088. [PubMed: 17158942]
148. Lewin C, Doherty C, Govan J. In vitro activities of meropenem, PD 127391, PD 131628, ceftazidime, chloramphenicol, co-trimoxazole, and ciprofloxacin against Pseudomonas cepacia. Antimicrob Agents Chemother. 1993; 37(1):123–125. [PubMed: 8431009]
149. Manno G, Ugolotti E, Belli ML, Fenu ML, Romano L, Cruciani M. Use of the E test to assess synergy of antibiotic combinations against isolates of Burkholderia cepacia-complex from patients with cystic fibrosis. Eur J Clin Microbiol Infect Dis. 2003; 22(1):28–34. [PubMed: 12582741]
150. Avgeri SG, Matthaiou DK, Dimopoulos G, Grammatikos AP, Falagas ME. Therapeutic options for Burkholderia cepacia infections beyond co-trimoxazole: a systematic review of the clinical evidence. Int J Antimicrob Agents. 2009; 33(5):394–404. [PubMed: 19097867]
151. Tullis DE, Burns JL, Retsch-Bogart GZ, et al. Inhaled aztreonam for chronic Burkholderia infection in cystic fibrosis: a placebo-controlled trial. J Cyst Fibros. 2014; 13(3):296–305. [PubMed: 24176390]
152. Woods CW, Bressler AM, LiPuma JJ, et al. Virulence associated with outbreak-related strains of Burkholderia cepacia complex among a cohort of patients with bacteremia. Clin Infect Dis. 2004; 38(9):1243–1250. [PubMed: 15127335]
153. Mahenthiralingam E, Baldwin A, Dowson CG. Burkholderia cepacia complex bacteria: opportunistic pathogens with important natural biology. J Appl Microbiol. 2008; 104(6):1539–1551. [PubMed: 18217926]
154. Govan JR, Brown PH, Maddison J, et al. Evidence for transmission of Pseudomonas cepacia by social contact in cystic fibrosis. Lancet. 1993; 342(8862):15–19. [PubMed: 7686239]
155. Clode FE, Kaufmann ME, Malnick H, Pitt TL. Distribution of genes encoding putative transmissibility factors among epidemic and nonepidemic strains of Burkholderia cepacia from cystic fibrosis patients in the United Kingdom. J Clin Microbiol. 2000; 38(5):1763–1766. [PubMed: 10790095]
156. France MW, Dodd ME, Govan JR, Doherty CJ, Webb AK, Jones AM. The changing epidemiology of Burkholderia species infection at an adult cystic fibrosis centre. J Cyst Fibros. 2008; 7(5):368–372. [PubMed: 18276200]
157. Koch C, Frederiksen B, Høiby N. Patient cohorting and infection control. Semin Respir Crit Care Med. 2003; 24(6):703–716. [PubMed: 16088586]

158. McDowell A, Mahenthiralingam E, Dunbar KE, Moore JE, Crowe M, Elborn JS. Epidemiology of Burkholderia cepacia complex species recovered from cystic fibrosis patients: issues related to patient segregation. J Med Microbiol. 2004; 53(Pt 7):663–668. [PubMed: 15184539]

159. Johansen HK, Kovesi TA, Koch C, Corey M, Høiby N, Levison H. Pseudomonas aeruginosa and Burkholderia cepacia infection in cystic fibrosis patients treated in Toronto and Copenhagen. Pediatr Pulmonol. 1998; 26(2):89–96. [PubMed: 9727758]

160. Saiman L, Macdonald N, Burns JL, Hoiby N, Speert DP, Weber D. Infection control in cystic fibrosis: practical recommendations for the hospital, clinic, and social settings. Am J Infect Control. 2000; 28(5):381–385. [PubMed: 11029140]

161. Conway S. Segregation is good for patients with cystic fibrosis. J R Soc Med. 2008; 101(Suppl 1):S31–S35. [PubMed: 18607016]

162. Paul ML, Pegler MA, Benn RA. Molecular epidemiology of Burkholderia cepacia in two Australian cystic fibrosis centres. J Hosp Infect. 1998; 38(1):19–26. [PubMed: 9513065]

163. Solé A, Salavert M. Fungal infections after lung transplantation. Transplant Rev (Orlando). 2008; 22(2):89–104. [PubMed: 18631862]

164. Nunley DR, Ohori P, Grgurich WF, et al. Pulmonary aspergillosis in cystic fibrosis lung transplant recipients. Chest. 1998; 114(5):1321–1329. [PubMed: 9824009]

165. Liu M, Worley S, Mallory GB Jr, et al. Fungal infections in pediatric lung transplant recipients: colonization and invasive disease. J Heart Lung Transplant. 2009; 28(11):1226–1230. [PubMed: 19782585]

166. Iversen M, Burton CM, Vand S, et al. Aspergillus infection in lung transplant patients: incidence and prognosis. Eur J Clin Microbiol Infect Dis. 2007; 26(12):879–886. [PubMed: 17874329]

167. Singh N, Husain S. Aspergillus infections after lung transplantation: clinical differences in type of transplant and implications for management. J Heart Lung Transplant. 2003; 22(3):258–266. [PubMed: 12633692]

168. Cahill BC, Hibbs JR, Savik K, et al. Aspergillus airway colonization and invasive disease after lung transplantation. Chest. 1997; 112(5):1160–1164. [PubMed: 9367451]

169. Mehrad B, Paciocco G, Martinez FJ, Ojo TC, Iannettoni MD, Lynch JP III. Spectrum of Aspergillus infection in lung transplant recipients: case series and review of the literature. Chest. 2001; 119(1):169–175. [PubMed: 11157600]

170. Minari A, Husni R, Avery RK, et al. The incidence of invasive aspergillosis among solid organ transplant recipients and implications for prophylaxis in lung transplants. Transpl Infect Dis. 2002; 4(4):195–200. [PubMed: 12535262]

171. Solé A, Morant P, Salavert M, Pemán J, Morales P. Valencia Lung Transplant Group. Aspergillus infections in lung transplant recipients: risk factors and outcome. Clin Microbiol Infect. 2005; 11(5):359–365. [PubMed: 15819861]

172. Paterson DL, Singh N. Invasive aspergillosis in transplant recipients. Medicine (Baltimore). 1999; 78(2):123–138. [PubMed: 10195093]

173. Liu JC, Modha DE, Gaillard EA. What is the clinical significance of filamentous fungi positive sputum cultures in patients with cystic fibrosis? J Cyst Fibros. 2013; 12(3):187–193. [PubMed: 23491855]

174. Helmi M, Love RB, Welter D, Cornwell RD, Meyer KC. Aspergillus infection in lung transplant recipients with cystic fibrosis: risk factors and outcomes comparison to other types of transplant recipients. Chest. 2003; 123(3):800–808. [PubMed: 12628881]

175. Luong ML, Chaparro C, Stephenson A, et al. Pretransplant Aspergillus colonization of cystic fibrosis patients and the incidence of post-lung transplant invasive aspergillosis. Transplantation. 2014; 97(3):351–357. [PubMed: 24305637]

176. de Vrankrijker AM, van der Ent CK, van Berkhout FT, et al. Aspergillus fumigatus colonization in cystic fibrosis: implications for lung function? Clin Microbiol Infect. 2011; 17(9):1381–1386. [PubMed: 21087348]

177. Egan JJ, Yonan N, Carroll KB, Deiraniya AK, Webb AK, Woodcock AA. Allergic bronchopulmonary aspergillosis in lung allograft recipients. Eur Respir J. 1996; 9(1):169–171. [PubMed: 8834350]

178. Jubin V, Ranque S, Stremler Le Bel N, Sarles J, Dubus JC. Risk factors for Aspergillus colonization and allergic bronchopulmonary aspergillosis in children with cystic fibrosis. Pediatr Pulmonol. 2010; 45(8):764–771. [PubMed: 20597074]

179. Paugam A, Baixench MT, Demazes-Dufeu N, et al. Characteristics and consequences of airway colonization by filamentous fungi in 201 adult patients with cystic fibrosis in France. Med Mycol. 2010; 48(Suppl 1):S32–S36. [PubMed: 21067327]

180. Shoseyov D, Brownlee KG, Conway SP, Kerem E. Aspergillus bronchitis in cystic fibrosis. Chest. 2006; 130(1):222–226. [PubMed: 16840406]

181. Pappas PG, Alexander BD, Andes DR, et al. Invasive fungal infections among organ transplant recipients: results of the Transplant-Associated Infection Surveillance Network (TRANS-NET). Clin Infect Dis. 2010; 50(8):1101–1111. [PubMed: 20218876]

182. Bhaskaran A, Hosseini-Moghaddam SM, Rotstein C, Husain S. Mold infections in lung transplant recipients. Semin Respir Crit Care Med. 2013; 34(3):371–379. [PubMed: 23821511]

183. Husni RN, Gordon SM, Longworth DL, et al. Cytomegalovirus infection is a risk factor for invasive aspergillosis in lung transplant recipients. Clin Infect Dis. 1998; 26(3):753–755. [PubMed: 9524855]

184. Husain S, Paterson DL, Studer S, et al. Voriconazole prophylaxis in lung transplant recipients. Am J Transplant. 2006; 6(12):3008–3016. [PubMed: 17062003]

185. Westney GE, Kesten S, De Hoyos A, Chapparro C, Winton T, Maurer JR. Aspergillus infection in single and double lung transplant recipients. Transplantation. 1996; 61(6):915–919. [PubMed: 8623160]

186. Goldfarb NS, Avery RK, Goormastic M, et al. Hypogammaglobulinemia in lung transplant recipients. Transplantation. 2001; 71(2):242–246. [PubMed: 11213067]

187. Mead L, Danziger-Isakov LA, Michaels MG, Goldfarb S, Glanville AR, Benden C. International Pediatric Lung Transplant Collaborative (IPLTC). Antifungal prophylaxis in pediatric lung transplantation: an international multicenter survey. Pediatr Transplant. 2014; 18(4):393–397. [PubMed: 24802346]

188. Avery RK. Antifungal prophylaxis in lung transplantation. Semin Respir Crit Care Med. 2011; 32(6):717–726. [PubMed: 22167399]

189. Kramer MR, Denning DW, Marshall SE, et al. Ulcerative tracheobronchitis after lung transplantation. A new form of invasive aspergillosis. Am Rev Respir Dis. 1991; 144(3 Pt 1): 552–556. [PubMed: 1654038]

190. Wu N, Huang Y, Li Q, Bai C, Huang HD, Yao XP. Isolated invasive Aspergillus tracheobronchitis: a clinical study of 19 cases. Clin Microbiol Infect. 2010; 16(6):689–695. [PubMed: 19689467]

191. Nunley DR, Gal AA, Vega JD, Perlino C, Smith P, Lawrence EC. Saprophytic fungal infections and complications involving the bronchial anastomosis following human lung transplantation. Chest. 2002; 122(4):1185–1191. [PubMed: 12377840]

192. Fernández-Ruiz M, Silva JT, San-Juan R, et al. Aspergillus tracheobronchitis: report of 8 cases and review of the literature. Medicine (Baltimore). 2012; 91(5):261–273. [PubMed: 22932790]

193. Neofytos D, Fishman JA, Horn D, et al. Epidemiology and outcome of invasive fungal infections in solid organ transplant recipients. Transpl Infect Dis. 2010; 12(3):220–229. [PubMed: 20113459]

194. Pihet M, Carrere J, Cimon B, et al. Occurrence and relevance of filamentous fungi in respiratory secretions of patients with cystic fibrosis—a review. Med Mycol. 2009; 47(4):387–397. [PubMed: 19107638]

195. Park SY, Kim SH, Choi SH, et al. Clinical and radiological features of invasive pulmonary aspergillosis in transplant recipients and neutropenic patients. Transpl Infect Dis. 2010; 12(4): 309–315. [PubMed: 20202177]

196. Husain S, Kwak EJ, Obman A, et al. Prospective assessment of Platelia Aspergillus galactomannan antigen for the diagnosis of invasive aspergillosis in lung transplant recipients. Am J Transplant. 2004; 4(5):796–802. [PubMed: 15084177]

197. Husain S, Paterson DL, Studer SM, et al. Aspergillus galactomannan antigen in the bronchoalveolar lavage fluid for the diagnosis of invasive aspergillosis in lung transplant recipients. Transplantation. 2007; 83(10):1330–1336. [PubMed: 17519782]

198. Luong ML, Clancy CJ, Vadnerkar A, et al. Comparison of an Aspergillus real-time polymerase chain reaction assay with galactomannan testing of bronchoalvelolar lavage fluid for the diagnosis of invasive pulmonary aspergillosis in lung transplant recipients. Clin Infect Dis. 2011; 52(10):1218–1226. [PubMed: 21507918]

199. Hadjiliadis D, Sporn TA, Perfect JR, Tapson VF, Davis RD, Palmer SM. Outcome of lung transplantation in patients with mycetomas. Chest. 2002; 121(1):128–134. [PubMed: 11796441]

200. Billaud EM, Guillemain R, Berge M, et al. Pharmacological considerations for azole antifungal drug management in cystic fibrosis lung transplant patients. Med Mycol. 2010; 48(Suppl 1):S52–S59. [PubMed: 21067331]

201. Han K, Capitano B, Bies R, et al. Bioavailability and population pharmacokinetics of voriconazole in lung transplant recipients. Antimicrob Agents Chemother. 2010; 54(10):4424–4431. [PubMed: 20679503]

202. Thompson GR III, Patterson TF. Pulmonary aspergillosis: recent advances. Semin Respir Crit Care Med. 2011; 32(6):673–681. [PubMed: 22167395]

203. Baddley JW, Andes DR, Marr KA, et al. Factors associated with mortality in transplant patients with invasive aspergillosis. Clin Infect Dis. 2010; 50(12):1559–1567. [PubMed: 20450350]

204. Steinbach WJ, Marr KA, Anaissie EJ, et al. Clinical epidemiology of 960 patients with invasive aspergillosis from the PATH Alliance registry. J Infect. 2012; 65(5):453–464. [PubMed: 22898389]

205. Herbrecht R, Denning DW, Patterson TF, et al. Invasive Fungal Infections Group of the European Organisation for Research and Treatment of Cancer and the Global Aspergillus Study Group. Voriconazole versus amphotericin B for primary therapy of invasive aspergillosis. N Engl J Med. 2002; 347(6):408–415. [PubMed: 12167683]

206. Singh N, Limaye AP, Forrest G, et al. Combination of voriconazole and caspofungin as primary therapy for invasive aspergillosis in solid organ transplant recipients: a prospective, multicenter, observational study. Transplantation. 2006; 81(3):320–326. [PubMed: 16477215]

207. Walsh TJ, Anaissie EJ, Denning DW, et al. Infectious Diseases Society of America. Treatment of aspergillosis: clinical practice guidelines of the Infectious Diseases Society of America. Clin Infect Dis. 2008; 46(3):327–360. [PubMed: 18177225]

208. Steinbach WJ, Stevens DA. Review of newer antifungal and immunomodulatory strategies for invasive aspergillosis. Clin Infect Dis. 2003; 37(Suppl 3):S157–S187. [PubMed: 12975751]

209. Chen J, Chan C, Colantonio D, Seto W. Therapeutic drug monitoring of voriconazole in children. Ther Drug Monit. 2012; 34(1):77–84. [PubMed: 22210097]

210. Brett J, Chong O, Graham GG, et al. Antifungal use and therapeutic monitoring of plasma concentrations of itraconazole in heart and lung transplantation patients. Ther Drug Monit. 2013; 35(1):133–136. [PubMed: 23188182]

211. Mitsani D, Nguyen MH, Shields RK, et al. Prospective, observational study of voriconazole therapeutic drug monitoring among lung transplant recipients receiving prophylaxis: factors impacting levels of and associations between serum troughs, efficacy, and toxicity. Antimicrob Agents Chemother. 2012; 56(5):2371–2377. [PubMed: 22330924]

212. Viscoli C, Herbrecht R, Akan H, et al. Infectious Disease Group of the EORTC. An EORTC Phase II study of caspofungin as first-line therapy of invasive aspergillosis in haematological patients. J Antimicrob Chemother. 2009; 64(6):1274–1281. [PubMed: 19841031]

213. Hiemenz JW, Raad II, Maertens JA, et al. Efficacy of caspofungin as salvage therapy for invasive aspergillosis compared to standard therapy in a historical cohort. Eur J Clin Microbiol Infect Dis. 2010; 29(11):1387–1394. [PubMed: 20703506]

214. Heinz WJ, Egerer G, Lellek H, Boehme A, Greiner J. Posaconazole after previous antifungal therapy with voriconazole for therapy of invasive Aspergillus disease, a retrospective analysis. Mycoses. 2013; 56(3):304–310. [PubMed: 23170837]

215. Ullmann AJ, Lipton JH, Vesole DH, et al. Posaconazole or fluconazole for prophylaxis in severe graft-versus-host disease. N Engl J Med. 2007; 356(4):335–347. [PubMed: 17251530]

216. Cornely OA, Maertens J, Winston DJ, et al. Posaconazole vs. fluconazole or itraconazole prophylaxis in patients with neutropenia. N Engl J Med. 2007; 356(4):348–359. [PubMed: 17251531]
217. Mihu CN, Kassis C, Ramos ER, Jiang Y, Hachem RY, Raad II. Does combination of lipid formulation of amphotericin B and echino-candins improve outcome of invasive aspergillosis in hematological malignancy patients? Cancer. 2010; 116(22):5290–5296. [PubMed: 20665889]
218. 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(8):1903–1911. [PubMed: 19459819]
219. Weigt SS, Copeland CA, Derhovanessian A, et al. Colonization with small conidia Aspergillus species is associated with bronchiolitis obliterans syndrome: a two-center validation study. Am J Transplant. 2013; 13(4):919–927. [PubMed: 23398785]
220. Husain S, Zaldonis D, Kusne S, Kwak EJ, Paterson DL, McCurry KR. Variation in antifungal prophylaxis strategies in lung transplantation. Transpl Infect Dis. 2006; 8(4):213–218. [PubMed: 17116134]
221. Neoh CF, Snell GI, Kotsimbos T, et al. Antifungal prophylaxis in lung transplantation—a world-wide survey. Am J Transplant. 2011; 11(2):361–366. [PubMed: 21272239]
222. Schaenman JM. Is universal antifungal prophylaxis mandatory in lung transplant patients? Curr Opin Infect Dis. 2013; 26(4):317–325. [PubMed: 23743815]
223. Tofte N, Jensen C, Tvede M, Andersen CB, Carlsen J, Iversen M. Use of prophylactic voriconazole for three months after lung transplantation does not reduce infection with Aspergillus: a retrospective study of 147 patients. Scand J Infect Dis. 2012; 44(11):835–841. [PubMed: 22803836]
224. Reichenspurner H, Gamberg P, Nitschke M, et al. Significant reduction in the number of fungal infections after lung-, heart-lung, and heart transplantation using aerosolized amphotericin B prophylaxis. Transplant Proc. 1997; 29(1–2):627–628. [PubMed: 9123449]
225. Drew RH, Dodds Ashley E, Benjamin DK Jr, Duane Davis R, Palmer SM, Perfect JR. Comparative safety of amphotericin B lipid complex and amphotericin B deoxycholate as aerosolized antifungal prophylaxis in lung-transplant recipients. Transplantation. 2004; 77(2): 232–237. [PubMed: 14742987]
226. Monforte V, Ussetti P, Gavaldà J, et al. Feasibility, tolerability, and outcomes of nebulized liposomal amphotericin B for Aspergillus infection prevention in lung transplantation. J Heart Lung Transplant. 2010; 29(5):523–530. [PubMed: 20061165]
227. Cadena J, Levine DJ, Angel LF, et al. Antifungal prophylaxis with voriconazole or itraconazole in lung transplant recipients: hepatotoxicity and effectiveness. Am J Transplant. 2009; 9(9):2085–2091. [PubMed: 19645709]
228. Lowry CM, Marty FM, Vargas SO, et al. Safety of aerosolized liposomal versus deoxycholate amphotericin B formulations for prevention of invasive fungal infections following lung transplantation: a retrospective study. Transpl Infect Dis. 2007; 9(2):121–125. [PubMed: 17461997]
229. Eriksson M, Lemström K, Suojaranta-Ylinen R, et al. Control of early Aspergillus mortality after lung transplantation: outcome and risk factors. Transplant Proc. 2010; 42(10):4459–4464. [PubMed: 21168718]
230. Koo S, Kubiak DW, Issa NC, et al. A targeted peritransplant antifungal strategy for the prevention of invasive fungal disease after lung transplantation: a sequential cohort analysis. Transplantation. 2012; 94(3):281–286. [PubMed: 22790447]
231. Singh N, Husain S. AST Infectious Diseases Community of Practice. Aspergillosis in solid organ transplantation. Am J Transplant. 2013; 13(Suppl 4):228–241. [PubMed: 23465016]
232. Zwald FO, Spratt M, Lemos BD, et al. Duration of voriconazole exposure: an independent risk factor for skin cancer after lung transplantation. Dermatol Surg. 2012; 38(8):1369–1374. [PubMed: 22551390]
233. Vadnerkar A, Nguyen MH, Mitsani D, et al. Voriconazole exposure and geographic location are independent risk factors for squamous cell carcinoma of the skin among lung transplant recipients. J Heart Lung Transplant. 2010; 29(11):1240–1244. [PubMed: 20591690]

234. Singer JP, Boker A, Metchnikoff C, et al. High cumulative dose exposure to voriconazole is associated with cutaneous squamous cell carcinoma in lung transplant recipients. J Heart Lung Transplant. 2012; 31(7):694–699. [PubMed: 22484291]

235. Palmer SM, Perfect JR, Howell DN, et al. Candidal anastomotic infection in lung transplant recipients: successful treatment with a combination of systemic and inhaled antifungal agents. J Heart Lung Transplant. 1998; 17(10):1029–1033. [PubMed: 9811413]

236. Hadjiliadis D, Howell DN, Davis RD, et al. Anastomotic infections in lung transplant recipients. Ann Transplant. 2000; 5(3):13–19. [PubMed: 11147024]

237. Almyroudis NG, Sutton DA, Linden P, Rinaldi MG, Fung J, Kusne S. Zygomycosis in solid organ transplant recipients in a tertiary transplant center and review of the literature. Am J Transplant. 2006; 6(10):2365–2374. [PubMed: 16925570]

238. Neofytos D, Treadway S, Ostrander D, et al. Epidemiology, outcomes, and mortality predictors of invasive mold infections among transplant recipients: a 10-year, single-center experience. Transpl Infect Dis. 2013; 15(3):233–242. [PubMed: 23432974]

239. Quan C, Spellberg B. Mucormycosis, pseudallescheriasis, and other uncommon mold infections. Proc Am Thorac Soc. 2010; 7(3):210–215. [PubMed: 20463250]

240. Neto FM, Camargo PC, Costa AN, et al. Fungal infection by Mucorales order in lung transplantation: 4 case reports. Transplant Proc. 2014; 46(6):1849–1851. [PubMed: 25131052]

241. Herbrecht R, Kessler R, Kravanja C, Meyer MH, Waller J, Letscher-Bru V. Successful treatment of Fusarium proliferatum pneumonia with posaconazole in a lung transplant recipient. J Heart Lung Transplant. 2004; 23(12):1451–1454. [PubMed: 15607679]

242. Sampathkumar P, Paya CV. Fusarium infection after solid-organ transplantation. Clin Infect Dis. 2001; 32(8):1237–1240. [PubMed: 11283817]

243. Tamm M, Malouf M, Glanville A. Pulmonary scedosporium infection following lung transplantation. Transpl Infect Dis. 2001; 3(4):189–194. [PubMed: 11844150]

244. Musk M, Chambers D, Chin W, Murray R, Gabbay E. Successful treatment of disseminated scedosporium infection in 2 lung transplant recipients: review of the literature and recommendations for management. J Heart Lung Transplant. 2006; 25(10):1268–1272. [PubMed: 17045941]

245. Raj R, Frost AE. Scedosporium apiospermum fungemia in a lung transplant recipient. Chest. 2002; 121(5):1714–1716. [PubMed: 12006471]

246. Symoens F, Knoop C, Schrooyen M, et al. Disseminated Scedosporium apiospermum infection in a cystic fibrosis patient after double-lung transplantation. J Heart Lung Transplant. 2006; 25(5): 603–607. [PubMed: 16678041]

247. Morio F, Horeau-Langlard D, Gay-Andrieu F, et al. Disseminated Scedosporium/Pseudallescheria infection after double-lung transplantation in patients with cystic fibrosis. J Clin Microbiol. 2010; 48(5):1978–1982. [PubMed: 20220160]

248. Castiglioni B, Sutton DA, Rinaldi MG, Fung J, Kusne S. Pseudallescheria boydii (Anamorph Scedosporium apiospermum). Infection in solid organ transplant recipients in a tertiary medical center and review of the literature. Medicine (Baltimore). 2002; 81(5):333–348. [PubMed: 12352630]

249. Cimon B, Carrère J, Vinatier JF, Chazalette JP, Chabasse D, Bouchara JP. Clinical significance of Scedosporium apiospermum in patients with cystic fibrosis. Eur J Clin Microbiol Infect Dis. 2000; 19(1):53–56. [PubMed: 10706182]

250. Hartmann C, Müller C, Weißbrodt H, et al. Successful prevention of scedosporiosis after lung transplantation in a cystic fibrosis patient by combined local and systemic triazole therapy. Med Mycol Case Rep. 2013; 2:116–118. [PubMed: 24432232]

251. Russell GK, Gadhok R, Simmonds NJ. The destructive combination of Scediosporium apiosperum lung disease and exuberant inflammation in cystic fibrosis. Paediatr Respir Rev. 2013; 14(Suppl 1):22–25. [PubMed: 23518310]

252. Hamilos G, Samonis G, Kontoyiannis DP. Pulmonary mucormycosis. Semin Respir Crit Care Med. 2011; 32(6):693–702. [PubMed: 22167397]

253. Cavusoglu C, Cicek-Saydam C, Karasu Z, et al. Mycobacterium tuberculosis infection and laboratory diagnosis in solid-organ transplant recipients. Clin Transplant. 2002; 16(4):257–261. [PubMed: 12099981]

254. Shitrit D, Bendayan D, Saute M, Kramer MR. Multidrug resistant tuberculosis following lung transplantation: treatment with pulmonary resection. Thorax. 2004; 59(1):79–80. [PubMed: 14694255]

255. Malouf MA, Glanville AR. The spectrum of mycobacterial infection after lung transplantation. Am J Respir Crit Care Med. 1999; 160(5 Pt 1):1611–1616. [PubMed: 10556129]

256. Lee J, Yew WW, Wong CF, Wong PC, Chiu CS. Multidrug-resistant tuberculosis in a lung transplant recipient. J Heart Lung Transplant. 2003; 22(10):1168–1173. [PubMed: 14550827]

257. Singh N, Paterson DL. Mycobacterium tuberculosis infection in solid-organ transplant recipients: impact and implications for management. Clin Infect Dis. 1998; 27(5):1266–1277. [PubMed: 9827281]

258. Muñoz P, Rodríguez C, Bouza E. Mycobacterium tuberculosis infection in recipients of solid organ transplants. Clin Infect Dis. 2005; 40(4):581–587. [PubMed: 15712081]

259. Miller RA, Lanza LA, Kline JN, Geist LJ. Mycobacterium tuberculosis in lung transplant recipients. Am J Respir Crit Care Med. 1995; 152(1):374–376. [PubMed: 7599848]

260. Aguilar-Guisado M, Givaldá J, Ussetti P, et al. RESITRA cohort. Pneumonia after lung transplantation in the RESITRA Cohort: a multicenter prospective study. Am J Transplant. 2007; 7(8):1989–1996. [PubMed: 17617864]

261. Olivier KN, Weber DJ, Lee JH, et al. Nontuberculous Mycobacteria in Cystic Fibrosis Study Group. Nontuberculous mycobacteria. II: nested-cohort study of impact on cystic fibrosis lung disease. Am J Respir Crit Care Med. 2003; 167(6):835–840. [PubMed: 12433669]

262. Olivier KN, Weber DJ, Wallace RJ Jr, et al. Nontuberculous Mycobacteria in Cystic Fibrosis Study Group. Nontuberculous mycobacteria. I: multicenter prevalence study in cystic fibrosis. Am J Respir Crit Care Med. 2003; 167(6):828–834. [PubMed: 12433668]

263. Leung JM, Olivier KN. Nontuberculous mycobacteria in patients with cystic fibrosis. Semin Respir Crit Care Med. 2013; 34(1):124–134. [PubMed: 23460012]

264. Oliver A, Maiz L, Cantón R, Escobar H, Baquero F, Gómez-Mampaso E. Nontuberculous mycobacteria in patients with cystic fibrosis. Clin Infect Dis. 2001; 32(9):1298–1303. [PubMed: 11303264]

265. Razvi S, Saiman L. Nontuberculous mycobacteria in cystic fibrosis. Pediatr Infect Dis J. 2007; 26(3):263–264. [PubMed: 17484227]

266. Levy I, Grisaru-Soen G, Lerner-Geva L, et al. Multicenter cross-sectional study of nontuberculous mycobacterial infections among cystic fibrosis patients, Israel. Emerg Infect Dis. 2008; 14(3):378–384. [PubMed: 18325250]

267. Bar-On O, Mussaffi H, Mei-Zahav M, et al. Increasing nontuberculous mycobacteria infection in cystic fibrosis. J Cyst Fibros. 2015; 14(1):53–62. [PubMed: 24917112]

268. Qvist T, Gilljam M, Jonsson B, et al. Epidemiology of nontuberculous mycobacteria among patients with cystic fibrosis in Scandinavia. J Cyst Fibros. 2015; 14(1):46–52. [PubMed: 25178871]

269. Chernenko SM, Humar A, Hutcheon M, et al. Mycobacterium abscessus infections in lung transplant recipients: the international experience. J Heart Lung Transplant. 2006; 25(12):1447–1455. [PubMed: 17178340]

270. Kesten S, Chaparro C. Mycobacterial infections in lung transplant recipients. Chest. 1999; 115(3): 741–745. [PubMed: 10084486]

271. Chalermskulrat W, Sood N, Neuringer IP, et al. Non-tuberculous mycobacteria in end stage cystic fibrosis: implications for lung transplantation. Thorax. 2006; 61(6):507–513. [PubMed: 16601086]

272. Huang HC, Weigt SS, Derhovanessian A, et al. Non-tuberculous mycobacterium infection after lung transplantation is associated with increased mortality. J Heart Lung Transplant. 2011; 30(7): 790–798. [PubMed: 21482148]

273. Sermet-Gaudelus I, Le Bourgeois M, Pierre-Audigier C, et al. Mycobacterium abscessus and children with cystic fibrosis. Emerg Infect Dis. 2003; 9(12):1587–1591. [PubMed: 14720400]

274. Roux AL, Catherinot E, Ripoll F, et al. Jean-Louis Herrmann for the OMA Group. Multicenter study of prevalence of nontuberculous mycobacteria in patients with cystic fibrosis in France. J Clin Microbiol. 2009; 47(12):4124–4128. [PubMed: 19846643]

275. Hjelte L, Petrini B, Källenius G, Strandvik B. Prospective study of mycobacterial infections in patients with cystic fibrosis. Thorax. 1990; 45(5):397–400. [PubMed: 2382245]

276. Whittaker LA, Teneback C. Atypical mycobacterial and fungal infections in cystic fibrosis. Semin Respir Crit Care Med. 2009; 30(5):539–546. [PubMed: 19760541]

277. Efthimiou J, Smith MJ, Hodson ME, Batten JC. Fatal pulmonary infection with Mycobacterium fortuitum in cystic fibrosis. Br J Dis Chest. 1984; 78(3):299–302. [PubMed: 6743529]

278. Fairhurst RM, Kubak BM, Shpiner RB, Levine MS, Pegues DA, Ardehali A. Mycobacterium abscessus empyema in a lung transplant recipient. J Heart Lung Transplant. 2002; 21(3):391–394. [PubMed: 11897529]

279. Sanguinetti M, Ardito F, Fiscarelli E, et al. Fatal pulmonary infection due to multidrug-resistant Mycobacterium abscessus in a patient with cystic fibrosis. J Clin Microbiol. 2001; 39(2):816–819. [PubMed: 11158161]

280. Doucette K, Fishman JA. Nontuberculous mycobacterial infection in hematopoietic stem cell and solid organ transplant recipients. Clin Infect Dis. 2004; 38(10):1428–1439. [PubMed: 15156482]

281. Torres F, Hodges T, Zamora MR. Mycobacterium marinum infection in a lung transplant recipient. J Heart Lung Transplant. 2001; 20(4):486–489. [PubMed: 11295588]

282. Taylor JL, Palmer SM. Mycobacterium abscessus chest wall and pulmonary infection in a cystic fibrosis lung transplant recipient. J Heart Lung Transplant. 2006; 25(8):985–988. [PubMed: 16890122]

283. Muñoz RM, Alonso-Pulpón L, Yebra M, Segovia J, Gallego JC, Daza RM. Intestinal involvement by nontuberculous mycobacteria after heart transplantation. Clin Infect Dis. 2000; 30(3):603–605. [PubMed: 10722455]

284. Griffith DE, Aksamit T, Brown-Elliott BA, et al. ATS Mycobacterial Diseases Subcommittee; American Thoracic Society; Infectious Disease Society of America. An official ATS/IDSA statement: diagnosis, treatment, and prevention of nontuberculous mycobacterial diseases. Am J Respir Crit Care Med. 2007; 175(4):367–416. [PubMed: 17277290]

285. Sugihara E, Hirota N, Niizeki T, et al. Usefulness of bronchial lavage for the diagnosis of pulmonary disease caused by Mycobacterium avium-intracellulare complex (MAC) infection. J Infect Chemother. 2003; 9(4):328–332. [PubMed: 14691654]

286. Koh WJ, Lee KS, Kwon OJ, Jeong YJ, Kwak SH, Kim TS. Bilateral bronchiectasis and bronchiolitis at thin-section CT: diagnostic implications in nontuberculous mycobacterial pulmonary infection. Radiology. 2005; 235(1):282–288. [PubMed: 15703315]

287. Ellis SM. The spectrum of tuberculosis and non-tuberculous mycobacterial infection. Eur Radiol. 2004; 14(Suppl 3):E34–E42. [PubMed: 14749960]

288. Trulock EP, Bolman RM, Genton R. Pulmonary disease caused by Mycobacterium chelonae in a heart-lung transplant recipient with obliterative bronchiolitis. Am Rev Respir Dis. 1989; 140(3): 802–805. [PubMed: 2506786]

289. Baldi S, Rapellino M, Ruffini E, Cavallo A, Mancuso M. Atypical mycobacteriosis in a lung transplant recipient. Eur Respir J. 1997; 10(4):952–954. [PubMed: 9150340]

290. Gilljam M, Scherstén H, Silverborn M, Jönsson B, Ericsson Hollsing A. Lung transplantation in patients with cystic fibrosis and Mycobacterium abscessus infection. J Cyst Fibros. 2010; 9(4): 272–276. [PubMed: 20400381]

291. Robinson PD, Harris KA, Aurora P, Hartley JC, Tsang V, Spencer H. Paediatric lung transplant outcomes vary with Mycobacterium abscessus complex species. Eur Respir J. 2013; 41(5):1230–1232. [PubMed: 23633613]

292. Aitken ML, Limaye A, Pottinger P, et al. Respiratory outbreak of Mycobacterium abscessus subspecies massiliense in a lung transplant and cystic fibrosis center. Am J Respir Crit Care Med. 2012; 185(2):231–232. [PubMed: 22246710]

293. 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(5):452–460. [PubMed: 22676720]

294. Zaidi S, Elidemir O, Heinle JS, et al. Mycobacterium abscessus in cystic fibrosis lung transplant recipients: report of 2 cases and risk for recurrence. Transpl Infect Dis. 2009; 11(3):243–248. [PubMed: 19298240]
295. Griffith DE, Aksamit TR. Therapy of refractory nontuberculous mycobacterial lung disease. Curr Opin Infect Dis. 2012; 25(2):218–227. [PubMed: 22327466]
296. Colin AA. Eradication of mycobacterium abscessus in a chronically infected patient with cystic fibrosis. Pediatr Pulmonol. 2000; 30(3):267–268. [PubMed: 10973047]
297. Radhakrishnan DK, Yau Y, Corey M, et al. Non-tuberculous mycobacteria in children with cystic fibrosis: isolation, prevalence, and predictors. Pediatr Pulmonol. 2009; 44(11):1100–1106. [PubMed: 19830845]
298. Saiman L, Siegel J. Cystic Fibrosis Foundation Consensus Conference on Infection Control Participants. Infection control recommendations for patients with cystic fibrosis: Microbiology, important pathogens, and infection control practices to prevent patient-to-patient transmission. Am J Infect Control. 2003; 31(3, Suppl):S1–S62. [PubMed: 12762292]
299. Kendall BA, Winthrop KL. Update on the epidemiology of pulmonary nontuberculous mycobacterial infections. Semin Respir Crit Care Med. 2013; 34(1):87–94. [PubMed: 23460008]
300. Bange FC, Brown BA, Smaczny C, Wallace RJ Jr, Böttger EC. Lack of transmission of mycobacterium abscessus among patients with cystic fibrosis attending a single clinic. Clin Infect Dis. 2001; 32(11):1648–1650. [PubMed: 11340540]
301. Bryant JM, Grogono DM, Greaves D, et al. Whole-genome sequencing to identify transmission of Mycobacterium abscessus between patients with cystic fibrosis: a retrospective cohort study. Lancet. 2013; 381(9877):1551–1560. [PubMed: 23541540]
302. Davidson RM, Reynolds PR, Farias-Hesson E, Duarte RS, Jackson M, Strong M. Genome Sequence of an Epidemic Isolate of Mycobacterium abscessus subsp. bolletii from Rio de Janeiro Brazil. Genome announcements. 2013:1.
303. Tettelin H, Davidson RM, Agrawal S, et al. High-level relatedness among Mycobacterium abscessus subsp. massiliense strains from widely separated outbreaks. Emerg Infect Dis. 2014; 20(3):364–371. [PubMed: 24565502]
304. Manuel O, Kumar D, Singer LG, Cobos I, Humar A. Incidence and clinical characteristics of herpes zoster after lung transplantation. J Heart Lung Transplant. 2008; 27(1):11–16. [PubMed: 18187081]
305. Clark NM, Lynch JP III, Sayah D, Belperio JA, Fishbein MC, Weigt SS. DNA viral infections complicating lung transplantation. Semin Respir Crit Care Med. 2013; 34(3):380–404. [PubMed: 23821512]
306. Lehto JT, Halme M, Tukiainen P, Harjula A, Sipponen J, Lautenschlager I. Human herpesvirus-6 and -7 after lung and heart-lung transplantation. J Heart Lung Transplant. 2007; 26(1):41–47. [PubMed: 17234516]
307. Weigt SS, Gregson AL, Deng JC, Lynch JP III, Belperio JA. Respiratory viral infections in hematopoietic stem cell and solid organ transplant recipients. Semin Respir Crit Care Med. 2011; 32(4):471–493. [PubMed: 21858751]
308. Chamnan P, Shine BS, Haworth CS, Bilton D, Adler AI. Diabetes as a determinant of mortality in cystic fibrosis. Diabetes Care. 2010; 33(2):311–316. [PubMed: 19918014]
309. Moran A, Dunitz J, Nathan B, Saeed A, Holme B, Thomas W. Cystic fibrosis-related diabetes: current trends in prevalence, incidence, and mortality. Diabetes Care. 2009; 32(9):1626–1631. [PubMed: 19542209]
310. Milla CE, Billings J, Moran A. Diabetes is associated with dramatically decreased survival in female but not male subjects with cystic fibrosis. Diabetes Care. 2005; 28(9):2141–2144. [PubMed: 16123480]
311. Moran A, Brunzell C, Cohen RC, et al. CFRD Guidelines Committee. Clinical care guidelines for cystic fibrosis-related diabetes: a position statement of the American Diabetes Association and a clinical practice guideline of the Cystic Fibrosis Foundation, endorsed by the Pediatric Endocrine Society. Diabetes Care. 2010; 33(12):2697–2708. [PubMed: 21115772]

312. 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(6):773–778. [PubMed: 16313324]

313. Hofer M, Schmid C, Benden C, et al. Diabetes mellitus and survival in cystic fibrosis patients after lung transplantation. J Cyst Fibros. 2012; 11(2):131–136. [PubMed: 22112935]

314. Heisel O, Heisel R, Balshaw R, Keown P. New onset diabetes mellitus in patients receiving calcineurin inhibitors: a systematic review and meta-analysis. Am J Transplant. 2004; 4(4):583–595. [PubMed: 15023151]

315. Aris RM, Neuringer IP, Weiner MA, Egan TM, Ontjes D. Severe osteoporosis before and after lung transplantation. Chest. 1996; 109(5):1176–1183. [PubMed: 8625663]

316. Donovan DS Jr, Papadopoulos A, Staron RB, et al. Bone mass and vitamin D deficiency in adults with advanced cystic fibrosis lung disease. Am J Respir Crit Care Med. 1998; 157(6 Pt 1):1892–1899. [PubMed: 9620924]

317. Cahill BC, O'Rourke MK, Parker S, Stringham JC, Karwande SV, Knecht TP. Prevention of bone loss and fracture after lung transplantation: a pilot study. Transplantation. 2001; 72(7):1251–1255. [PubMed: 11602851]

318. Legroux-Gérot I, Leroy S, Prudhomme C, et al. Bone loss in adults with cystic fibrosis: prevalence, associated factors, and usefulness of biological markers. Joint Bone Spine. 2012; 79(1):73–77. [PubMed: 21733729]

319. Sheikh S, Gemma S, Patel A. Factors associated with low bone mineral density in patients with cystic fibrosis. J Bone Miner Metab. 2014

320. Hecker TM, Aris RM. Management of osteoporosis in adults with cystic fibrosis. Drugs. 2004; 64(2):133–147. [PubMed: 14717616]

321. Spira A, Gutierrez C, Chaparro C, Hutcheon MA, Chan CK. Osteoporosis and lung transplantation: a prospective study. Chest. 2000; 117(2):476–481. [PubMed: 10669693]

322. Aris RM, Renner JB, Winders AD, et al. Increased rate of fractures and severe kyphosis: sequelae of living into adulthood with cystic fibrosis. Ann Intern Med. 1998; 128(3):186–193. [PubMed: 9454526]

323. Aris RM, Lester GE, Renner JB, et al. Efficacy of pamidronate for osteoporosis in patients with cystic fibrosis following lung transplantation. Am J Respir Crit Care Med. 2000; 162(3 Pt 1): 941–946. [PubMed: 10988110]

324. Conwell LS, Chang AB. Bisphosphonates for osteoporosis in people with cystic fibrosis. Cochrane Database Syst Rev. 2014; 3:CD002010. [PubMed: 24627308]

325. Gelfond D, Borowitz D. Gastrointestinal complications of cystic fibrosis. Clin Gastroenterol Hepatol. 2013; 11(4):333–342. quiz e30–e31. [PubMed: 23142604]

326. Borowitz D, Gelfond D. Intestinal complications of cystic fibrosis. Curr Opin Pulm Med. 2013; 19(6):676–680. [PubMed: 24060981]

327. Shah N, Tan HL, Sebire N, Suri R, Leuven K. The role of endoscopy and biopsyin the managementof severe gastrointestinal disease in cystic fibrosis patients. Pediatr Pulmonol. 2013; 48(12):1181–1189. [PubMed: 23825099]

328. Pauwels A, Blondeau K, Dupont LJ, Sifrim D. Mechanisms of increased gastroesophageal reflux in patients with cystic fibrosis. Am J Gastroenterol. 2012; 107(9):1346–1353. [PubMed: 22777342]

329. Gilljam M, Chaparro C, Tullis E, Chan C, Keshavjee S, Hutcheon M. GI complications after lung transplantation in patients with cystic fibrosis. Chest. 2003; 123(1):37–41. [PubMed: 12527600]

330. Young LR, Hadjiliadis D, Davis RD, Palmer SM. Lung transplantation exacerbates gastroesophageal reflux disease. Chest. 2003; 124(5):1689–1693. [PubMed: 14605036]

331. Lubetkin EI, Lipson DA, Palevsky HI, et al. GI complications after orthotopic lung transplantation. Am J Gastroenterol. 1996; 91(11):2382–2390. [PubMed: 8931422]

332. Benden C, Aurora P, Curry J, Whitmore P, Priestley L, Elliott MJ. High prevalence of gastroesophageal reflux in children after lung transplantation. Pediatr Pulmonol. 2005; 40(1):68–71. [PubMed: 15880421]

333. Subhi R, Ooi R, Finlayson F, et al. Distal intestinal obstruction syndrome in cystic fibrosis: presentation, outcome and management in a tertiary hospital (2007–2012). ANZ J Surg. 2014; 84(10):740–744. [PubMed: 24237857]
334. Farrelly PJ, Charlesworth C, Lee S, Southern KW, Baillie CT. Gastrointestinal surgery in cystic fibrosis: a 20-year review. J Pediatr Surg. 2014; 49(2):280–283. [PubMed: 24528967]
335. Parisi GF, Di Dio G, Franzonello C, et al. Liver disease in cystic fibrosis: an update. Hepat Mon. 2013; 13(8):e11215. [PubMed: 24171010]
336. Herrmann U, Dockter G, Lammert F. Cystic fibrosis-associated liver disease. Best Pract Res Clin Gastroenterol. 2010; 24(5):585–592. [PubMed: 20955961]
337. Bhardwaj S, Canlas K, Kahi C, et al. Hepatobiliary abnormalities and disease in cystic fibrosis: epidemiology and outcomes through adulthood. J Clin Gastroenterol. 2009; 43(9):858–864. [PubMed: 19525864]
338. Pokorny CS, Bye PT, MacLeod C, Selby WS. Antibiotic-associated colitis and cystic fibrosis. Dig Dis Sci. 1992; 37(9):1464–1468. [PubMed: 1505297]
339. Rivlin J, Lerner A, Augarten A, Wilschanski M, Kerem E, Ephros MA. Severe Clostridium difficile-associated colitis in young patients with cystic fibrosis. J Pediatr. 1998; 132(1):177–179. [PubMed: 9470027]
340. Mylonakis E, Ryan ET, Calderwood SB. Clostridium difficile—Associated diarrhea: A review. Arch Intern Med. 2001; 161(4):525–533. [PubMed: 11252111]
341. Lee JT, Hertz MI, Dunitz JM, et al. The rise of Clostridium difficile infection in lung transplant recipients in the modern era. Clin Transplant. 2013; 27(2):303–310. [PubMed: 23316931]
342. Nagakumar P. Pseudomembranous colitis in cystic fibrosis. Paediatr Respir Rev. 2013; 14(Suppl 1):26–27. [PubMed: 23601208]
343. Yates B, Murphy DM, Fisher AJ, et al. Pseudomembranous colitis in four patients with cystic fibrosis following lung transplantation. BMJ Case Rep. 2009; 2009:xx.
344. Madill J, Gutierrez C, Grossman J, et al. Toronto Lung Transplant Program. 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(3):288–296. [PubMed: 11257554]
345. Singer LG, Brazelton TR, Doyle RL, Morris RE, Theodore J. International Lung Transplant Database Study Group. Weight gain after lung transplantation. J Heart Lung Transplant. 2003; 22(8):894–902. [PubMed: 12909470]
346. Hollander FM, van Pierre DD, de Roos NM, van de Graaf EA, Iestra JA. Effects of nutritional status and dietetic interventions on survival in Cystic Fibrosis patients before and after lung transplantation. J Cyst Fibros. 2014; 13(2):212–218. [PubMed: 24041590]
347. Armitage JM, Kormos RL, Stuart RS, et al. Posttransplant lymphoproliferative disease in thoracic organ transplant patients: ten years of cyclosporine-based immunosuppression. J Heart Lung Transplant. 1991; 10(6):877–886. discussion 886–887. [PubMed: 1661607]
348. Randhawa PS, Jaffe R, Demetris AJ, et al. Expression of Epstein-Barr virus-encoded small RNA (by the EBER-1 gene) in liver specimens from transplant recipients with post-transplantation lymphoproliferative disease. N Engl J Med. 1992; 327(24):1710–1714. [PubMed: 1331789]
349. Cohen AH, Sweet SC, Mendeloff E, et al. High incidence of posttransplant lymphoproliferative disease in pediatric patients with cystic fibrosis. Am J Respir Crit Care Med. 2000; 161(4 Pt 1): 1252–1255. [PubMed: 10764320]
350. Aris RM, Maia DM, Neuringer IP, et al. Post-transplantation lymphoproliferative disorder in the Epstein-Barr virus-naïve lung transplant recipient. Am J Respir Crit Care Med. 1996; 154(6 Pt 1):1712–1717. [PubMed: 8970360]
351. Kotloff RM, Ahya VN. Medical complications of lung transplantation. Eur Respir J. 2004; 23(2): 334–342. [PubMed: 14979513]
352. Maisonneuve P, FitzSimmons SC, Neglia JP, Campbell PW III, Lowenfels AB. Cancer risk in nontransplanted and transplanted cystic fibrosis patients: a 10-year study. J Natl Cancer Inst. 2003; 95(5):381–387. [PubMed: 12618503]
353. 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(2):122–129. [PubMed: 23178438]

354. Schöni MH, Maisonneuve P, Schöni-Affolter F, Lowenfels AB. CF/CSG Group. Cancer risk in patients with cystic fibrosis: the European data. J R Soc Med. 1996; 89(Suppl 27):38–43. [PubMed: 8778449]

355. Rousseau A, Monchaud C, Debord J, et al. Bayesian forecasting of oral cyclosporin pharmacokinetics in stable lung transplant recipients with and without cystic fibrosis. Ther Drug Monit. 2003; 25(1):28–35. [PubMed: 12548141]

356. Knoop C, Vervier I, Thiry P, et al. Cyclosporine pharmacokinetics and dose monitoring after lung transplantation: comparison between cystic fibrosis and other conditions. Transplantation. 2003; 76(4):683–688. [PubMed: 12973109]

357. Brugière O, Thabut G, Castier Y, et al. Lung retransplantation for bronchiolitis obliterans syndrome: long-term follow-up in a series of 15 recipients. Chest. 2003; 123(6):1832–1837. [PubMed: 12796157]

358. Aigner C, Jaksch P, Taghavi S, et al. Pulmonary retransplantation: is it worth the effort? A long-term analysis of 46 cases. J Heart Lung Transplant. 2008; 27(1):60–65. [PubMed: 18187088]

359. Kawut SM, Lederer DJ, Keshavjee S, et al. Outcomes after lung retransplantation in the modern era. Am J Respir Crit Care Med. 2008; 177(1):114–120. [PubMed: 17901410]

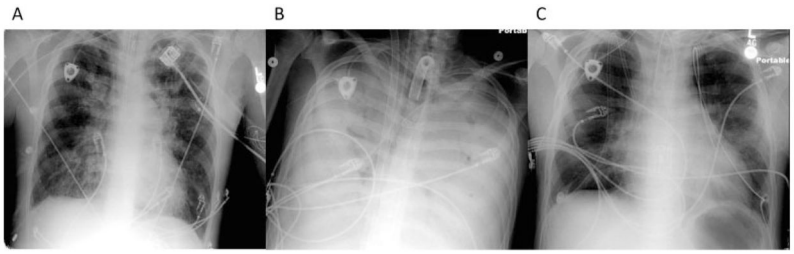

Fig. 1.

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.

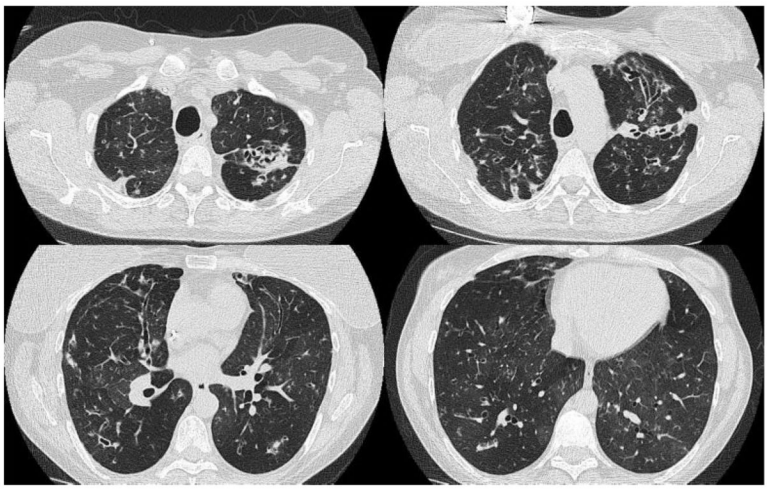

Fig. 2.

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.

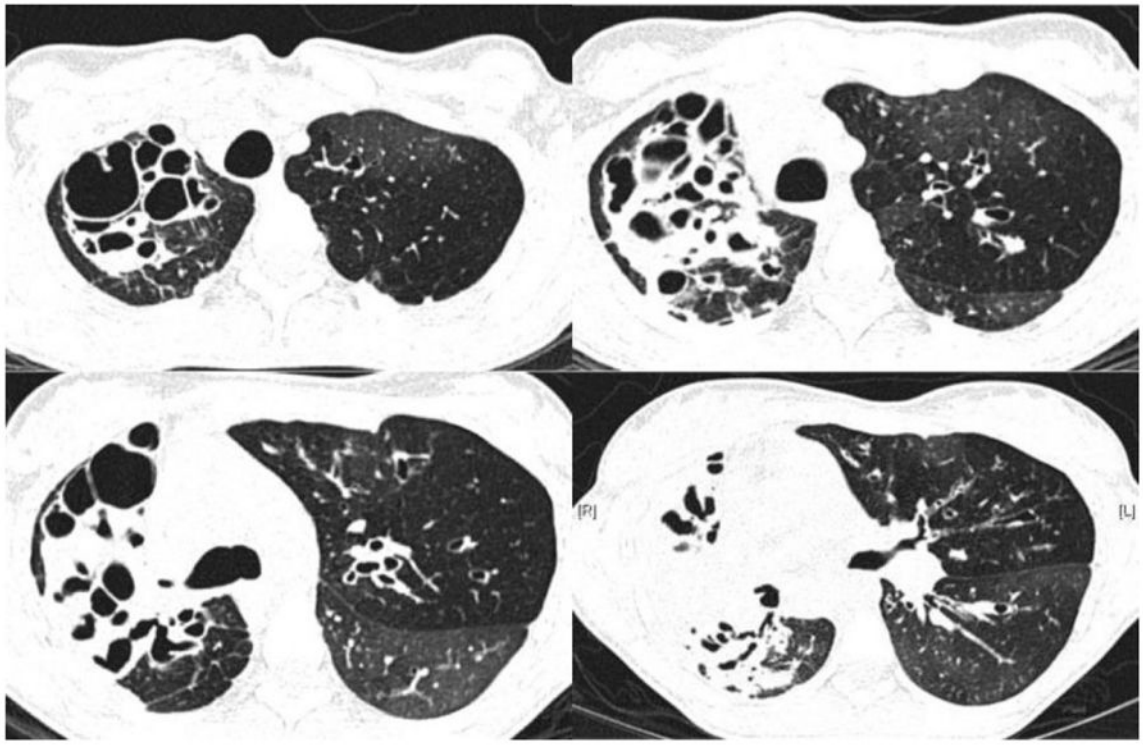

Fig. 3.

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.

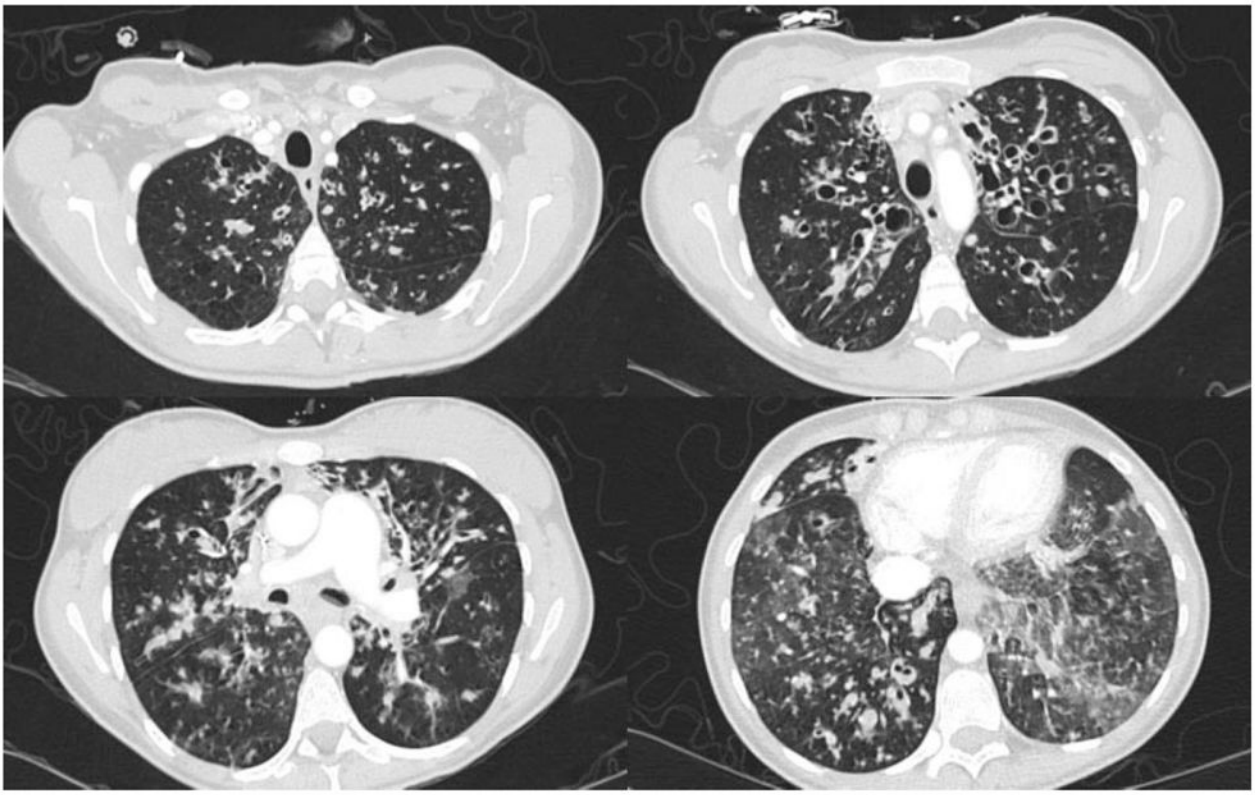

Fig. 4.

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.

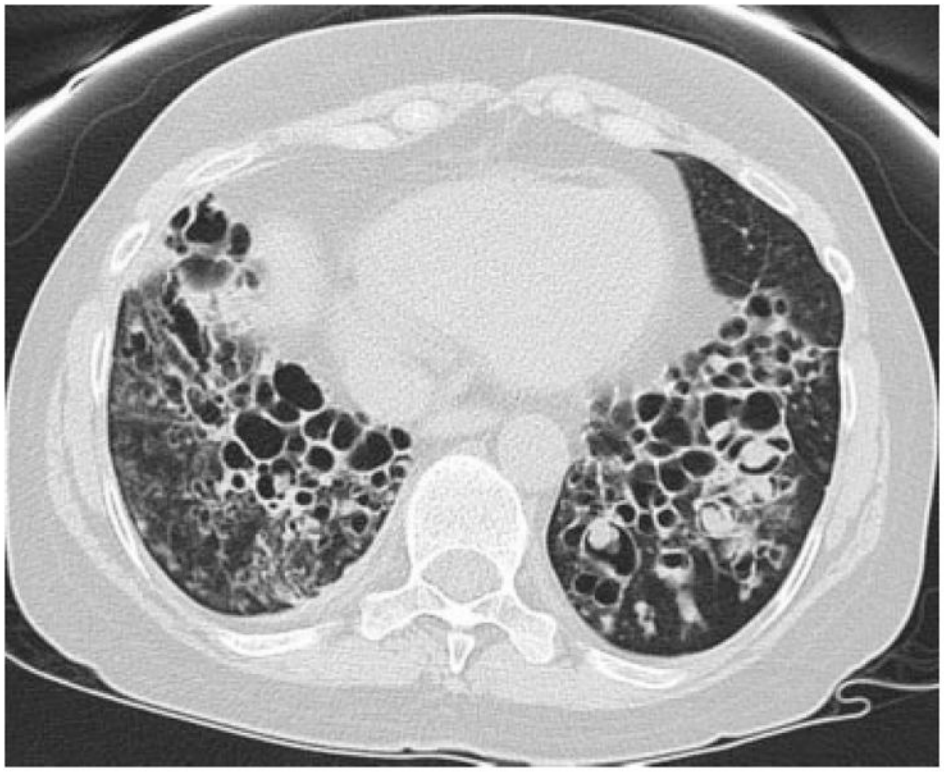

Fig. 5.
Chest CT of a 56-year-old woman with cystic fibrosis that demonstrates multiple mycetomas occupying ectatic airways, most prominently in the left lung.

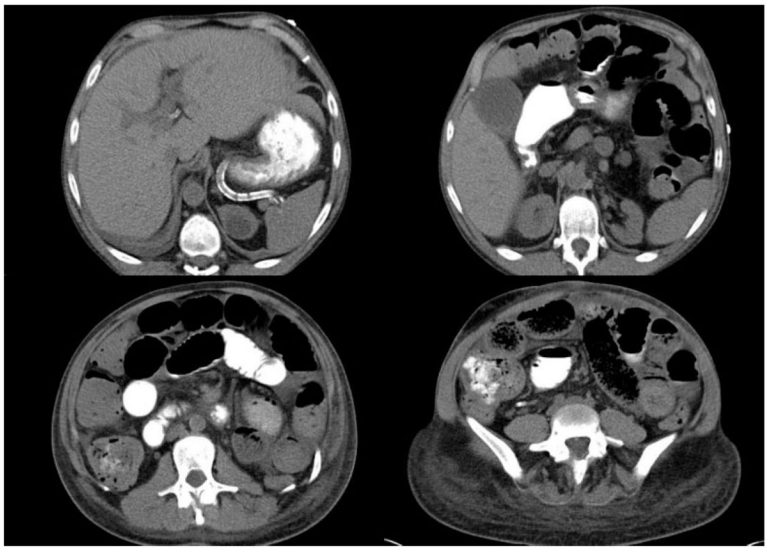

Fig. 6.

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; FEV_1, forced expiratory volume in 1 second.

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