Lung Transplantation for Advanced Bronchiectasis

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ABSTRACT

Lung transplant (LT) can be successfully performed on patients with advanced bronchiectatic lung disease with subsequent good posttransplant quality of life and long-term outcome. Most of the data are derived from patients with cystic fibrosis (CF), but LT can be effective in patients with non-CF bronchiectasis as well. Despite the presence of chronic lower respiratory tract infection with bacterial pathogens in these patients pretransplant, posttransplant infections do not generally have significant impact on survival, although infection with antibiotic-resistant bacteria may complicate posttransplant management. Although benefit of LT for young children with CF is somewhat controversial, LT can clearly benefit older children and adults with advanced lung disease due to bronchiectasis. This article reviews indications (and contraindications) for LT, discusses particular problems that may arise posttransplant, and provides a rationale for referring patients with bronchiectasis for LT.

KEYWORDS: Cystic fibrosis, bronchiectasis, lung transplantation

Bronchiectasis is characterized by bronchial wall damage associated with a significant increase in airway diameter and has many causes[1,2] (Table 1). Virtually all patients with cystic fibrosis (CF) will eventually develop extensive and progressively worsening bronchiectasis. Although bronchiectasis is nearly always diffuse, it can occasionally be restricted to an isolated region of the lung in patients with non-CF bronchiectasis.

Patients with symptomatic bronchiectasis typically have inflammation in airway walls accompanied by chronic infection that can be associated with the presence of a variety of bacterial or fungal pathogens. Excessive production of abnormal mucus and impaired secretion clearance are typical manifestations of the disease. Defects in host defense mechanisms may heighten susceptibility to bronchial wall injury and chronic infection, and impaired injury repair mechanisms predispose patients to gradual progression and increasing severity of bronchiectasis. Bronchial wall and mucosal damage can, in turn, further impair host defense mechanisms. The clinical consequences of symptomatic bronchiectasis are chronic cough and expectoration of abnormal mucus, airflow obstruction that tends to be progressive, and persistent respiratory tract infection in the majority of patients.

Patients with advanced stages of bronchiectasis have poor quality of life (QoL) and are at increasing risk of death as their lung function progressively falls.[3–5]

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Lung transplantation can improve QoL and prolong survival for carefully selected patients with advanced bronchiectasis. Patients with CF accounted for 26% of bilateral lung transplants and 2% of single lung transplants performed between January 1995 and June 2008 (www.ishlt.org). During this same period patients with non-CF bronchiectasis accounted for 4.5% of all bilateral lung transplants and 0.4% of all single lung transplants.

PATHOBIOLOGY AND EPIDEMIOLOGY

Gene mutations that cause dysfunction of the CF transmembrane conduction regulator protein (CFTR) and lead to the spectrum of organ dysfunction that characterizes CF of the pancreas were described nearly 20 years ago.[6] However, a genetic basis for most other forms of bronchiectasis has not been determined. The incidence of CF varies greatly by ethnicity (1:3200 in Caucasians, 1:31,000 in Asian Americans, 1:15,000 in African Americans), and over 1500 CFTR mutations have been identified.[7] Although the pancreas is usually prominently affected and extensively damaged at birth for the majority of patients with CF (hence the name *CF of the pancreas*, which was eventually shortened to *CF*), patients with less severe mutations that do not impair the CFTR ion channel as much as the most severe mutations (e.g., ΔF508) may display fairly adequate pancreatic function along with better nutritional status and milder lung disease.[8] Newborns with CFTR dysfunction have essentially normal lungs at birth but may rapidly develop inflammation and infection that lead to progressive bronchiectasis, especially if mutations that lead to more severe CFTR dysfunction are present.

Once lung disease becomes established and bacteria are present in the lung, large numbers of neutrophils accumulate in the airways in both CF and non-CF bronchiectasis. Typical bacterial isolates in CF include *Haemophilus influenzae* and *Staphylococcus aureus* in infants and toddlers. *Pseudomonas aeruginosa* tends to make a later appearance and correlates with accelerated lung function decline once it becomes established in the airways, and over 80% of CF patients will eventually have chronic infection with this pathogen. Recent analyses of respiratory secretions and lung tissue in CF have shown that anaerobes such as *Provetella* may be present in relatively high numbers (but will not grow out on routine aerobic cultures of respiratory secretions).[9] The anaerobic environment in CF airways that are filled with secretions likely promotes the growth and persistence of anaerobes as well as the conversion of *P. aeruginosa* to mucoexopolysaccharide-producing biofilm organisms and their persistence in the lower respiratory tract.[10]

Non-CF bronchiectasis, which has been given orphan disease status, has been linked to many different abnormalities and causes (Table 1), but approximately a third of cases are idiopathic.[2] The underlying genetic defect or predisposing factors remain undefined for nearly all cases, with the exception of relatively uncommon causes such as primary ciliary dysfunction syndromes and α-1-antitrypsin deficiency. The bronchiectasis is sometimes focal (e.g., caused by focal necrotizing pneumonia, foreign body aspiration), but it is much more commonly diffuse. As in CF bronchiectasis, airway inflammation and bacterial infection are usually present in advanced disease with a predominance of neutrophils in airspace secretions. Excessive mucus production typically complicates the disease along with progressive airway obstruction. Patients who are homozygous for CFTR mutations may be misdiagnosed as having non-CF bronchiectasis (to be discussed).

DIAGNOSIS, NATURAL HISTORY, AND MANAGEMENT

Persistent productive cough is the most common symptom of bronchiectasis and is often accompanied by fatigue, dyspnea, and rhinosinusitis. Fatigue and lethargy can be prominent features in some patients and worsen with exacerbations. Crackles, and less commonly wheezing, may be heard on chest auscultation, but digital clubbing is now rarely present in patients with non-CF bronchiectasis. Up to a third of patients with non-CF bronchiectasis are diagnosed by primary care physicians as having COPD. Bronchiectasis shares several clinical features with COPD, including chronic cough, airflow obstruction, lower airway inflammation, and persistent sputum production leading to frequent office visits and hospitalizations. Some patients, including patients with some degree of reactive airways who have CF, may be misdiagnosed as having asthma.

A thorough history and examination should provide clues to the diagnosis. Conditions associated with bronchiectasis may be discovered by examining/evaluating skin and evaluating other organ systems. Although abnormalities may be discovered on plain chest x-rays (CXR) in up to 90% of patients, the CXR is typically nondiagnostic, and the gold standard diagnostic tool is the high-resolution computed tomographic (HRCT) scan. Laboratory testing should include complete blood count (CBC) with differential, complete metabolic panel, quantitative immunoglobulin levels, α-1-antitrypsin levels, sputum evaluation (bacterial, fungal, AFB [acid-fast bacilli]), and routine pulmonary function tests (PFTs). If CF is suspected, sweat testing for increased chloride levels and gene testing should be performed. Bronchoscopy is usually not indicated except to evaluate focal bronchiectasis to rule out an obstructing lesion or to localize significant and/or recurrent hemoptysis. Bronchoscopy may also be useful to rule out chronic nontuberculous mycobacterial infection (e.g., *Mycobacterium avium* complex) when multiple, peripheral nodules with

Table 1 Characteristics and Diagnosis of Specific Forms of Bronchiectasis (BE)

Condition/Disease	Clinical Characteristics	Diagnosis*
Cystic fibrosis	▪ Diffuse BE with predilection for upper lung regions	▪ Sweat chloride test positive
	▪ Pancreatic insufficiency in most	▪ Genotyping (2 CF alleles)
	▪ Recurrent/chronic lower respiratory tract infection (*P. aeruginosa* and *S. aureus* are most common isolates)	▪ Other testing may be necessary for mild mutations (sweat chloride may be normal in some patients)
	▪ Prominent paranasal sinus disease (most)	▪ ABPA can occur
	▪ High incidence of meconium ileus (infants)	
	▪ Infertility in males	
Allergic bronchopulmonary aspergillosis	▪ History of chronic asthma (usually)	▪ Positive skin prick test for AF (diagnostic)
	▪ CXR shows atelectasis	▪ Sputum culture → AF (supportive)
	▪ Peripheral blood eosinophilia	▪ ↑ ↑ Serum IgE level (supportive)
	▪ ↑ ↑ Serum IgE level	
Inherited immunodeficiency disorders	▪ Recurrent sinopulmonary infection	▪ IgG, IgA, IgM deficiency (or subclass deficiency)
		▪ Consider SCID, CVID, CGD
(Right) middle lobe syndrome (can occur in lingula of LUL)	▪ Recurrent RML (or lingula) pneumonia	▪ Bronchoscopy shows RML bronchus obstructed or narrowed/stenotic
		▪ HRCT may show lesion and/or BE
Primary ciliary dyskinesia (autosomal-recessive)	▪ Recurrent/chronic sinopulmonary infection	▪ Mucosal biopsy
	▪ May have situs inversus (Kartagener syndrome)	▪ Saccharin test (must have confirmatory mucosal biopsy if abnormal)
	▪ Male infertility	▪ Nasal nitric oxide (very low levels)
Young syndrome	▪ Recurrent sinopulmonary disease	▪ Rule out CF (sweat chloride) and ciliary dysfunction (normal cilia on biopsy)
	▪ Azoospermia	
	▪ Normal spermatogenesis	
Nontuberculous mycobacteria	▪ Respiratory symptoms c/w BE	▪ Sputum culture + (usually MAC)
	▪ HRCT → BE (especially RML/lingula, nodules, tree-in-bud opacities)	▪ Bronchoscopy may be necessary
Connective tissue disease (RA and SS >others)	▪ Respiratory symptoms c/w BE	▪ Criteria for CTD met
HIV/AIDS	▪ Respiratory symptoms c/w BE	▪ HIV testing
Alpha-1-antitrypsin deficiency	▪ Respiratory symptoms c/w BE	▪ Respiratory symptoms c/w BE
		▪ Detection of abnormal gene (e.g., *PiZZ*)
Interstitial lung disease	▪ Respiratory symptoms c/w BE	▪ Clinicoradiologic-pathologic diagnosis of specific interstitial lung disease
	▪ Sarcoidosis, IPF, other	
Inflammatory bowel disease	▪ Respiratory symptoms c/w BE	▪ HRCT shows BE
	▪ Crohn disease or UC present	
Postinfectious	▪ Respiratory symptoms c/w BE	▪ HRCT shows BE
	▪ History of measles, TB, pertussis, severe pneumonia, etc.	▪ Other etiology ruled out
Aspiration/GERD	▪ Respiratory symptoms c/w BE	▪ GI tract radiologic imaging, endoscopy
		▪ pH/impedance probe
		▪ Rule out other causes

Table 1 (*Continued*)

Condition/Disease	Clinical Characteristics	Diagnosis*
Localized BE	▪ Foreign body aspiration ▪ Airway tumors ▪ Airway stenosis	▪ Bronchoscopy should be performed

*High-resolution computed tomographic scanning (HRCT) should be performed to establish a confident diagnosis of bronchiectasis.
ABPA, allergic bronchopulmonary aspergillosis; AF, *A. fumigatus*; c/w, consistent with; CGD, chronic granulomatous disease; CTD, connective tissue disease; CVID, combined variable immunodeficiency; CXR, routine posteroanterior and lateral chest x-ray; GI, gastrointestinal; HIV, human immunodeficiency virus; Ig, immunoglobulin; IPF, idiopathic pulmonary fibrosis; LUL, left upper lobe; MAC, *Mycobacterium avium* complex; RA, rheumatoid arthritis; RML, right middle lobe; SCID, severe combined immunodeficiency; SS, Sjögren syndrome; TB, tuberculosis; UC, ulcerative colitis.

tree-in-bud opacities are present and sputum evaluation has been negative.

The median survival for patients with CF is 37 years in the United States; it is higher in other countries such as Denmark[11] and may be linked to aggressive surveillance and eradication protocols that target *P. aeruginosa*. Patients with CF can develop numerous complications that can lead to death (e.g., liver failure, colitis, vasculitis), but the majority of patients succumb to respiratory complications and respiratory failure. Patients with non-CF bronchiectasis can succumb to their disease at a young age, but this is uncommon, and many patients have fairly stable lung function and may have relatively mild bronchiectasis that remains stable for very prolonged periods of time. Many non-CF bronchiectasis patients have a normal life span, although their health-related QoL may be significantly impaired by their chronic lung disease and the treatments that its management may require.

Effective management of bronchiectasis consists of employing optimal suppressive antimicrobial strategies and maintenance therapies (e.g., chronic macrolide/azalide therapy, inhaled bronchodilators, inhaled corticosteroids) to minimize disease progression and prevent acute exacerbations (Table 2). Underlying disorders (e.g., immunoglobulin deficiency or α-1-antitrypsin deficiency) should be treated appropriately, if present. Optimal management of acute exacerbations and complications such as severe hemoptysis or pneumothorax is key to prolonging life and maintaining lung function, Bronchial artery embolization or surgical resection may be needed in concert with acute management for massive hemoptysis. Comorbidities [osteopenia/osteoporosis, diabetes, gastroesophageal reflux disease (GERD), malnutrition, cardiac dysfunction, sleep-disordered breathing, anemia, etc.] should be detected and treated as needed. Occasionally, performing surgical resection for truly focal bronchiectasis that has a significant impact on QoL may be appropriate.

REFERRAL FOR LUNG TRANSPLANTATION

Bilateral lung transplantation is recommended for suppurative lung disease resulting from CF or non-CF bronchiectasis if the disease is progressive and severe. CF is the third most common indication for which lung transplantation is performed.[12] If a single lung transplant is performed in these patients allowing a native infected lung to remain in place, conventional wisdom predicts that residual infection in the native lung would lead to complications in an immunocompromised recipient. Thus bilateral lung transplantation is recommended in advanced bronchiectasis. However, some single lung transplants have been performed with contralateral pneumonectomy. Lung transplantation is more commonly performed in CF-related bronchiectasis due to the high prevalence of severe bronchiectasis in CF as compared with non-CF etiologies. However, the overall prevalence of non-CF bronchiectasis in the United States is at least fivefold greater than that for patients with CF.

The timing for referral to be considered for lung transplantation in advanced bronchiectasis presents a considerable challenge for physicians, especially for young patients with CF. The most recently published guideline[13] for the selection of lung transplant candidates with CF gave specific criteria for referral of CF patients that included (1) forced expiratory volume in 1 second (FEV_1) below 30% predicted or a rapid decline in FEV_1, particularly in young female patients; (2) exacerbation of pulmonary disease requiring intensive care unit (ICU) admission; (3) increasing frequency of exacerbations requiring antibiotic therapy; (4) refractory and/or recurrent pneumothorax; and (5) recurrent hemoptysis not controlled by bronchial arterial embolization. Declining lung function with hypercapnea, resting hypoxemia and need for supplemental oxygen therapy, or significant pulmonary hypertension should prompt referral, and the International Society for Heart and Lung Transplantation (ISHLT) statement cited oxygen-dependent respiratory failure, hypercapnia, and pulmonary hypertension as the indications for proceeding with transplantation.[13] Although mechanical ventilation is considered a relative contraindication to lung transplantation, the committee recognized CF as an exception, and patients transplanted while receiving mechanical ventilation can do as well as patients not receiving such at the time of transplant.[14]

Various clinical assessments that correlate with prognosis can aid in determining when patients and their physicians should consider referral for transplantation (Table 3). Because specific guidelines for referral of

Table 2 Pretransplant Management of Bronchiectasis

Type of Therapy	Options
Chronic Management	
Antibiotics	▪ Oral (rotating/intermittent/chronic) ▪ Inhaled (e.g., tobramycin) ▪ Intravenous ▪ Chronic macrolide/azalide (antiinflammatory)
Secretion clearance	▪ Postural drainage and percussion (can cause or exacerbate GER) ▪ Vibrating vest ▪ Intermittent percussive ventilation (IPV) ▪ Positive expiratory pressure (PEP) ▪ Flutter valve ▪ Acapella device ▪ rhDNase (Pulmozyme, Genentech, Inc., South San Francisco, CA) for CF ▪ Hypertonic saline
Bronchodilators	▪ Short-acting β-agonists as indicated ▪ Long-acting β-agonists if indicated and therapeutic response evoked ▪ Consider anticholinergics
Antiinflammatory	▪ Chronic macrolide/azalide therapy ▪ Corticosteroids - inhaled (unclear benefit for CF) - oral (use judiciously, avoid chronic therapy if possible) ▪ NSAID (e.g., ibuprofen) - may be useful for CF (especially children) - may have significant toxicity (e.g., renal, GI tract)
Nutrition	▪ Pancreatic enzyme replacement as needed (CF) ▪ Optimize nutrition as needed ▪ Vitamin replacement (CF) ▪ Optimal treatment of diabetes if present
Supplemental oxygen	▪ Use only if indicated by standard criteria
Vaccinations	▪ Pneumococcus ▪ Influenza
Treatment of comorbidities	Screen and treat as appropriate (osteopenia/osteoporosis, diabetes, GERD, malnutrition, cardiac dysfunction, sleep-disordered breathing, paranasal sinus disease, anemia, etc.)
Acute Exacerbations	
Diagnostic evaluation	▪ History and thorough physical examination ▪ Sputum gram smear and culture/sensitivities (other microbiological evaluation as indicated) ▪ Chest radiograph (rule out new infiltrate, pneumothorax, other)
Antibiotics	▪ Intravenous therapy for moderate/severe illness ▪ Adjust initial empirical therapy for sensitivities of sputum bacterial isolates ▪ Consider double coverage of *P. aeruginosa* in patients with CF (can also cover non-CF patients if *P. aeruginosa* isolated or suspected)
Other therapies	▪ Bronchodilators (assess for clinical response) ▪ Corticosteroids (use judiciously) ▪ Supplemental oxygen ▪ Secretion clearance strategies (use carefully with severe exacerbations or if significant hemoptysis is present) ▪ Assisted ventilation as required (e.g., BiPAP)

BiPAP, bilevel positive airway pressure; GER, gastroesophageal reflux; GERD, gastroesophageal reflux disease; GI, gastrointestinal; IPV, intermittent percussive ventilation; NSAID, nonsteroidal antiinflammatory drug; PEP, positive expiratory pressure; GI, gastrointestinal.

Table 3 Predictors of Prognosis in CF and Non-CF Bronchiectasis

Parameter/Test	Findings
Pulmonary function testing	Decline and severe impairment of FEV_1 and FVC
Arterial blood gas testing	Resting hypoxemia
	Resting hypercarbia
Exercise evaluation (e.g., 6-minute walk test)	Oxyhemoglobin desaturation
	Reduced walk distance
	Need for supplemental oxygen
Right heart function	Pulmonary hypertension
Cardiac function	Resting tachycardia
	Depressed maximal oxygen uptake (exercise)
Metabolic abnormalities	Increased energy expenditure (CF)
	Diabetes mellitus (CF)
Rapid decline in lung function	Female patient (CF)
	Young age
Complications of bronchiectasis	Refractory pneumothorax
	Significant hemoptysis
	Frequent exacerbations
Poor nutrition	Low and declining weight for height (CF)
	Hypoalbuminemia

FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity.

patients with non-CF bronchiectasis have not been established, parameters similar to those set forth for CF patients can likely also be applied to patients with non-CF bronchiectasis (Table 4). Therefore, patients with declining lung function with parameters similar to those identified for patients with CF should be considered for referral if standard criteria[13] that preclude lung transplantation are absent. In general, patients with CF or non-CF bronchiectasis should be considered for transplantation if there is less than a 50% probability of survival for 2 years without transplant, QoL is likely to be improved by transplantation, there are no contraindications to transplantation, and patients are fully informed of the risks and benefits of lung transplant and fully committed to proceeding with evaluation and potential listing. Referred patients should have a rigorous evaluation to determine whether they meet criteria for being placed on the wait list and to identify comorbidities that can complicate management (Table 5).

Table 4 Indicators of End-Stage Lung Disease in Bronchiectasis

- Postbronchodilator FEV_1 <30% (especially young females with CF)
- Exacerbation of pulmonary disease requiring intensive care unit stay
- Increasing frequency of exacerbations requiring intravenous antibiotics
- Refractory and/or recurrent pneumothorax
- Recurrent hemoptysis not controlled by embolization
- Other factors to consider:
  - Hypercarbia ($PaCO_2$ >45 mm Hg)
  - Rapidly progressive decline in lung function
  - Resting hypoxemia (PaO_2 <55 mm Hg)

CF, cystic fibrosis; FEV_1, forced expiratory volume in 1 second; $PaCO_2$, partial pressure of carbon dioxide in arterial blood; PaO_2, partial pressure of oxygen in arterial blood.

Lung Transplant for CF Bronchiectasis

Because the majority of patients with CF dying in childhood and early adulthood succumb to advanced lung disease, various investigators have analyzed the utility of potential predictors for optimal timing for lung transplantation in this population. Kerem et al[15] published a landmark study in 1992 that identified FEV_1 in a cohort of 673 patients with CF as the single most predictive indicator of mortality in the CF population. An FEV_1 less than 30% of predicted was associated with a 2-year mortality rate of 50%. Additionally, among patients with the same FEV_1, the relative risk of death was 2.0 [95% confidence interval (CI), 1.5 to 2.6] in patients 10 years younger than other patients, and 2.2 (95% CI, 1.6 to 3.1) in female patients as compared with male patients. Based on this study, the original version of the ISHLT lung transplant candidate selection guidelines published in 1998 stated that patients with CF with a FEV_1 less than 30% of predicted be listed for lung transplantation, with consideration given to earlier referrals for female and young patients.[16]

Using a multivariate logistic regression model and information from the CF Foundation National Patient Registry on patients over 6 years of age, Mayer-Hamblett et al[17] reported that their data (derived from the largest collection of data available in CF) provided no better diagnostic accuracy than the simpler FEV_1 criterion

Table 5 Evaluation of Potential Lung Transplant Candidates with Advanced Bronchiectasis

Category	Specific Issues/Tests
Psychosocial evaluation	• ? Tobacco use within 6 months
	• ? Illicit drug use, drug-seeking behavior
	• ? Compliance with medical therapies
	• ? Significant psychiatric illness
	• ? Adequate social support
Cardiopulmonary	• High-resolution computed tomographic scan of thorax
	• Full pulmonary function tests
	• Standardized exercise test (e.g., 6-minute walk test)
	• Cardiac evaluation
	▪ Electrocardiogram
	▪ Stress echocardiogram
	▪ Cardiac catheterization (right and left)
	• Lipid profile
Infection-specific	• Quarterly respiratory tract cultures (for suppurative lung disease)
	▪ Gram-negative bacilli
	▪ Methicillin-resistant *S. aureus*
	▪ Mycobacteria
	▪ Fungi
	• Serology
	▪ Human immunodeficiency virus
	▪ Hepatitis B and C
	▪ *Varicella*
	▪ Cytomegalovirus
	▪ Toxoplasmosis
	• Vaccinations
	• Tuberculin skin test
	• Evaluation and treatment of paranasal sinus disease
Other	• Peripheral blood cell survey
	• Glucose and hemoglobin A_{1C}
	• 24-hour creatinine clearance
	• Bone mineral density scan
	• Evaluation of hepatic and renal function
	• Screening for gastroesophageal reflux

for referral for lung transplant. Rapid decline in the FEV_1 was found to be a predictor of poor outcome in patients with CF in two different studies,[18,19] and 1-year survival rates for patients with CF admitted to the ICU were reported as 52%.[19] Other studies, however, reported median survival rates of 3.9 and 4.6 years with an FEV_1 less than 30%,[20,21] and other criteria have been suggested as more useful indicators of progressive lung function decline and risk of death.[18,22–26]

Lung transplantation for young children with CF has been somewhat controversial. Liou and colleagues[27–29] analyzed the U.S. Cystic Fibrosis Foundation (CFF) Registry survival data and concluded that the majority of pediatric CF patients had equivocal or negative survival benefit from lung transplantation. On the basis of proportional-hazards modeling of wait-listed children who underwent transplantation between 1992 and 2002, Liou et al[27] concluded that only five of 514 wait-listed patients had clearly improved survival. This analysis and conclusion led to considerable discussion in the literature.[30–32] Criticisms of Liou et al's analysis include the use of registry data that were not updated at the time of transplantation (covariates used for modeling were obtained up to 2 years prior to listing, which would equate to 3 or more years prior to transplantation), not including many physiological markers used by transplant centers for predicting prognosis and making listing decisions, and the analysis of a cohort of patients wait-listed before the U.S. lung allocation scoring system was implemented.[32] This debate has led to an ongoing joint effort to identify parameters that predict the need for listing for lung transplantation and a high likelihood of net benefit for children with CF.

Lung Transplant for Non-CF Bronchiectasis

CF bronchiectasis has been studied much more extensively than non-CF bronchiectasis, especially in the area

of lung transplantation. Interestingly, in non-CF bronchiectasis, mutations in the *CFTR* gene may be linked to disease pathogenesis,[33] and some patients with CF may be misdiagnosed as having non-CF bronchiectasis. Ten of 50 (20%) of patients in this cohort of non-CF bronchiectasis had a de novo diagnosis of CF established after a comprehensive analysis was performed on this patient group that had been previously diagnosed as having non-CF bronchiectasis. Thirty *CFTR* mutations were identified in 24 patients (50% prevalence of abnormal *CFTR*).[33] Mutations that alter RNA splicing and/or functional chloride conductance were found to be common and likely contribute to the susceptibility and pathogenesis of adult bronchiectasis· These findings suggest that all patients with apparent non-CF bronchiectasis should undergo a comprehensive analysis to detect *CFTR* mutations, and some of these patients may be homozygous for *CFTR* mutations and qualify for a diagnosis of CF.

Because the number of lung transplants performed for patients with non-CF bronchiectasis is much smaller than for patients with CF, few data are available concerning patient selection, choice of procedure, and outcomes. Nonetheless, bilateral lung transplantation is widely accepted in this patient population with the assumption that infection in the contralateral native bronchiectatic lung would threaten single lung transplant.[34–37]

The current medical literature has only one study that examined lung transplantation for non-CF bronchiectasis.[38] This study included a total of 22 patients (12 men, 10 women) with an average age of 43.4 years (range 20 to 58) who underwent lung transplantation for non-CF bronchiectasis over a 13-year period. The underlying etiologies of bronchiectasis for 20 patients whose complete data were available included idiopathic for nine patients, childhood infection for eight, hypogammaglobulinemia for two, and immotile cilia syndrome for one. Bilateral sequential lung transplants were performed in four patients, double lung transplants with tracheal anastomosis in five, heart–lung transplants in six, and single lung transplant in seven. A total of 5/7 patients who underwent a single lung transplant had minimal sputum production, whereas 4/7 had asymmetric findings on CT scan of the chest.

INFECTION AND LUNG TRANSPLANTION FOR BRONCHIECTASIS

Chronic infection in bronchiectatic airways raises numerous concerns in the selection of candidates for lung transplantation. Although the presence of certain pathogens is not a contraindication for lung transplant for bronchiectasis, the presence of resistant pathogens would appear to contraindicate a surgical procedure that requires significant postimplantation immunosuppression and its attendant risk of opportunistic infection. However, patients with CF who undergo liver transplantation and are placed on subsequent immunosuppression and have typical CF lung disease can do very well[39–41] and may have improvement in their pulmonary function. These patients fare better than patients with simultaneous liver–lung transplantation in terms of outcomes.[41] These findings suggest that single lung transplant for suppurative bronchiectasis could be safely performed in selected patients. However, bilateral lung transplantation remains the procedure of choice, although contralateral pneumonectomy has been reported.[42,43]

P. aeruginosa is the most common pathogen leading to the decline and reduction in pulmonary function in both CF[17,18] and non-CF bronchiectasis.[44,45] However, chronic infections with other gram-negative organisms and *Staphylococcus aureus* are commonly associated with declining lung function and advanced bronchiectasis. Chronic therapy that targets these pathogens, particularly *P. aeruginosa*, often leads to antibiotic resistance. A retrospective study by Aris et al[46] of 66 transplanted patients (panresistant, *P. aeruginosa* ($n = 21$) and *Burkholderia cepacia* ($n = 6$) or sensitive, *P. aeruginosa* ($n = 39$)) over 6 years determined that 1-year survival for patients with panresistant *P. aeruginosa* was similar to that of patients with sensitive pathogens (81% and 83%, respectively; $p > 0.2$). These authors concluded that CF patients infected with panresistant *P. aeruginosa* had similar transplant outcomes as those patients with sensitive organisms and should not be excluded from candidacy for lung transplantation based solely on this criterion. More recently in 2007, Hadjiliadis et al[47] performed a retrospective study (University of Toronto and Duke) to determine the impact of panresistant bacteria on posttransplant outcome for patients with CF. A total of 45/103 (43.7%) patients in the study harbored panresistant bacteria (43 *P. aeruginosa*, one *Stenotrophomonas maltophilia*, and one *Achromobacter xylosoxidans*)· Using log-rank testing, the authors demonstrated a decreased survival in patients with panresistant bacteria compared with patients with sensitive bacteria ($88.6 \pm 4.8\%$ vs $96.6 \pm 2.4\%$ at 1 year and $58.3 \pm 9.2\%$ vs $85.6 \pm 5.2\%$ at 5 years). Despite these findings, the survival rates in patients with panresistant organisms were essentially identical to outcomes achieved for all transplant recipients with CF in the United States as published by the United Network for Organ Sharing (UNOS) registry. Further studies have also demonstrated that chronic infection with multidrug or panresistant *P. aeruginosa* has no significant influence on short-term survival outcome.[48,49]

Due to the lack of specific data regarding pretransplant colonization with methicillin-resistant *S. aureus* (MRSA) or other bacterial pathogens, multi- or panresistant nonfermenting gram-negative bacilli, such

as *S. maltophilia* and *A. xylosoxidans*, and *Aspergillus fumigatus* are not considered a contraindication to lung transplantation for CF.[13] Colonization with *A. fumigatus* is common in CF patients pretransplant.[50] If infection with *A. fumigatus* occurs posttransplant, it often occurs as tracheobronchial aspergillosis on the allograft bronchial epithelium, distal to the anastomoses where ischemic epithelium is susceptible to such infection.[50,51] *Scedosporium apiospermum* is an uncommon filamentous fungus that has been isolated from the lungs of some CF patients.[52] *Scedosporium* airway infection has been associated with airway complications, including early ischemic airway stenosis and bronchiolitis obliterans syndrome (BOS), and it can cause fatal infection.[53]

In addition to fungal infections, bronchiectatic airways are also susceptible to nontuberculous mycobacteria (NTM) infections. *Mycobacterium abscessus* has been recognized as a pathogen in CF. A survey administered to 31/62 transplant centers affiliated with the ISHLT to investigate the clinical significance of *M. abscessus* after lung transplantation[54] reported that two patients had *M. abscessus* respiratory colonization before lung transplantation, and the posttransplant incidence was 0.27%. The mortality of those patients with *M. abscessus* in the posttransplant period was 53.3%, with death partially attributed to infections other than *M. abscessus* and BOS.[26] More recently, Chalermskulrat et al[55] reported that the isolation of NTM before transplantation in CF patients should not be an exclusion criterion for lung transplantation, but it should alert physicians to patients at risk of recurrence following transplantation. This retrospective study identified 146 CF patients who underwent lung transplantation over a 13-year period. The prevalence rate of NTM prior to and after lung transplantation was 19.7% and 13.7%, respectively. The overall prevalence of invasive NTM disease after lung transplantation was low at 3.4% and was predicted most strongly by pretransplant NTM isolation; this association was restricted to *M. abscessus*. The NTM infections caused significant morbidity in a small number of patients after lung transplantation, but it was successfully treated and did not influence the posttransplant course. The presence of NTM infection is not a contraindication to lung transplantation, but not all lung transplant centers share this view.

The presence of certain subspecies of *B. cepacia* is considered a contraindication for lung transplant in patients with CF. Aris et al[46] demonstrated that the 6-month mortality was significantly increased from 12% to 33% if chronic infection with genomovar III of *B. cepacia* was present. Patients with panresistant *B. cepacia* also had a lower 1-year survival (50% vs 90%, $p < 0.05$) and had a higher mortality attributable to *B. cepacia* (50% vs 0%, $p < 0.01$) compared with patients with panresistant *P. aeruginosa*. In a retrospective study of 121 CF patients who underwent lung transplantation, Aris et al[56] demonstrated a significant increase in mortality, 33% compared with 12%, during the first 6 postoperative months in those patients infected preoperatively with *B. cepacia* complex compared with those who were not. Furthermore, 1-, 3-, and 5-year survival were significantly lower in the *B. cepacia* complex cohort. For those patients infected preoperatively, genomovar III patients were at the highest risk of *B. cepacia* complex–related mortality. The authors also reported that each of the *B. cepacia* complex–related deaths was caused by a unique genotype, using pulsed-field gel electrophoresis. Using Kaplan-Meier survival curves of transplanted and control patients stratified by 5-year predicted survival, Liou et al[57] reported that transplanted adult CF patients with *B. cepacia* infection derive no collective survival benefit from lung transplantation. Based on this medical literature, the majority of lung transplant centers in the United States exclude patients with *B. cepacia* infection from candidacy for lung transplantation. However, *B. cepacia* is not a single entity, but more a heterogeneous group of subspecies, commonly referred to as genomovars, which likely have a variable impact upon lung transplant outcomes. More recent studies have demonstrated that post–lung transplant mortality is likely attributed to *B. cenocepacia*, which was formerly known as genomovar III.[58] *B. gladioli* was also linked to greater posttransplant mortality as compared with uninfected transplant recipients.[59] Further studies are needed to identify transplant eligibility by better defining what *B. cepacia* complex subspecies are associated with higher mortality after lung transplantation.

OTHER CONSIDERATIONS

Deceased or cadaveric donation is the standard surgical procedure for lung transplantation, but due to a limited organ pool, there are other surgical options being addressed. There are growing interests in the use of donation after cardiac death (DCD) or non-heart-beating donors to increase the potential pool of donors as demand for transplants continues to grow. The use of DCD donor organs has led to successful transplantation, and the use of DCD donor lungs is slowly expanding.[60,61] Living-related lobar transplantation that typically uses a lower lobe from two donors (usually parents) to provide bilateral allografts has also been developed as a surgical option and performed on patients with CF. The recipient must have a thoracic cage with dimensions that can accommodate one lobe from each donor. In 2004, the 1-, 3-, and 5-year survival rates among living lobar recipients were reported as 70%, 54%, and 45%, respectively.[62]

Nonrespiratory medical complications that are commonly associated with CF need to be optimally treated prior to transplantation. These include chronic sinusitis, impaired nutrition, CF-related diabetes mellitus (CFRDM), gastroesophageal reflux (GER), liver

disease, and osteoporosis. If these problems are well controlled, they do not constitute contraindications for transplantation for patients with CF.[13] Endoscopic sinus surgery is frequently performed on CF patients prior to lung transplantation, but this treatment remains controversial. There are no data that strongly support a surgical approach (e.g., endoscopic sinus surgery), and medical management of paranasal sinus disease may be sufficient.[63,64]

Nutrition is an important issue among CF patients, and optimization of nutritional status can slow the rate of decline in lung function. Additionally, severe malnutrition with very low body mass index (BMI) increases the risk of poor outcome following transplantation. Nutritional depletion in lung transplant candidates was evaluated in 78 patients listed for lung transplantation, with 38% having CF or non-CF bronchiectasis.[65,66] Lean body mass depletion was associated with more severe hypoxemia, reduced 6-minute walk distance, and higher mortality while awaiting transplant. The duration of mechanical ventilation and time spent in the ICU following transplantation was linked to BMI, and survival was lowest in the group with weight $\geq$90% ideal body weight and creatinine height index $<$60%.[66] Supplemental nutrition via enteral feeding tube may be required prior to transplantation to improve BMI. A frequent contributing factor to lean body mass in CF patients is poor control of CFRDM. Optimal control in CFRDM can prevent lung disease progression in CF patients with early glucose derangements as noted in a recent study using glargine insulin.[67] After lung transplantation, CFRDM is further complicated by chronic prednisone therapy for immunosuppression. Nutritional failure may also be related to gastrointestinal complications due to GER, which is commonly present in CF patients.[68,69] After lung transplantation, GER persists or potentially worsens with a very high prevalence in rate demonstrated in both children[70] and adults.[71] Persistence of GER following transplantation may predispose recipients to developing bronchiolitis obliterans,[72,73] and measures should be taken to prevent GER in transplant recipients. Recipients with CF are also at increased risk for gastric bezoars[74] and distal intestinal obstruction syndrome (DIOS).[75] Additionally, numerous cases of pseudomembranous colitis due to *C. difficile* infection have been reported in recipients with CF.[76]

Limited data exist regarding hepatobiliary disease in CF. A recent retrospective study of 283 CF patients over a 32-year period identified that 5% of patients had CF-related hepatobiliary disease, with 93% of cases occurring in individuals before age 18 years.[77] Progression of CF-related liver disease is fairly uncommon, but patients can develop cirrhosis with portal hypertension.[78] Lung transplantation without liver transplantation was safely performed in patients with controlled portal hypertension and preserved hepatic function.[79] Reduced bone mineral density in CF was associated with several factors, including ΔF508 genotype, male sex, greater lung disease severity, and malnutrition.[80] While the diagnosis of CF is by itself a risk factor for developing low bone density, osteoporosis can progress following lung transplantation, due in large part to immunosuppressive therapy.[81]

PERIOPERATIVE AND EARLY POSTTRANSPLANT MANAGEMENT

Numerous complications of lung transplantation for CF or non-CF bronchiectasis can occur during the perioperative period.[82] Frequent complications seen in CF include hemorrhage, pulmonary edema, primary graft dysfunction, diaphragmatic paresis or paralysis, anastomotic stenosis or dehiscence, renal failure, stroke, and acute bacterial infection. Cardiopulmonary bypass and nitric oxide were required in 63.2% and 36.8% of patients, respectively. Lung allografts typically develop reperfusion injury characterized by pulmonary edema and inflammation.[83] The typical factors leading to postimplantation edema include patency of vascular anastomoses, disrupted lymphatics, and massive fluid resuscitation including blood products and crystalloid along with renal failure (if present). Krenn et al[84] reported that CF patients undergoing lung transplantation are possibly more susceptible to primary graft dysfunction (PGD) because of increased vascular endothelial growth factor-A (VEGF-A) expression, which mediates increased lung graft vascular permeability. The authors demonstrated that VEGF-A serum concentrations were higher in CF versus chronic obstructive pulmonary disease (COPD) patients ($p < 0.05$), and 60 minutes following reperfusion, donor lungs transplanted to CF patients had higher tissue water contents than in COPD patients ($p < 0.05$). However, the transplant indication of CF or non-CF bronchiectasis has not been linked to an increased incidence of primary graft dysfunction.

Bacterial infections frequently complicate the postoperative course of patients with bronchiectasis. Because numerous pathogens chronically dwell in the respiratory tract secretions of patients with chronic suppurative bronchiectasis, antibacterial agents are frequently used in the perioperative period after lung transplantation in addition to standard prophylactic/preemptive therapies given for viral (cytomegalovirus) and fungal (*A. fumigatus, P. jiroveci*) pathogens. However, antibacterial regimens can vary widely from center to center, and no controlled trials have been published that evaluate specific approaches to perioperative and postoperative antibacterial therapies. Most regimens include dual therapy that targets pathogens isolated from individual patients pre- and perioperatively, and combination therapy with more than one antibiotic class

is frequently used. Prophylactic regimens that utilize aerosolized antibiotics may also be used. Several transplant centers avoid intravenous tobramycin while patients are receiving tacrolimus or cyclosporine. Interestingly, tobramycin pharmacokinetics in CF patients appear to significantly change after lung transplantation.[85] Tobramycin clearance decreased 40%, volume of distribution increased 20%, elimination rate increased 52%, and half-life increased 141%, respectively, in posttransplant patients as compared with pretransplant.

POSTTRANSPLANT MONITORING AND SURVEILLANCE

CF patients have multiple organ system involvement that requires continued treatment following lung transplantation. Virtually all patients with CF have paranasal sinus disease, pancreatic exocrine insufficiency, and abnormal gastrointestinal motility. Additionally, they may have significant liver disease, osteoporosis, or diabetes. Non-CF bronchiectasis recipients may also have various comorbidities (e.g., osteoporosis, GERD, paranasal sinus disease) that require monitoring and treatment postoperatively.

Because of gastrointestinal dysfunction and malabsorption, patients with CF must have their calcineurin inhibitor (tacrolimus or cyclosporine A) levels monitored relatively frequently. Patients with CF require higher doses of tacrolimus than those without CF to achieve similar drug exposure.[86] Additionally, patients with CF also show a lower bioavailability of cyclosporine and a greater intrasubject variability of maximum concentration, concentration 2 hours after administration, and area under the curve.[87]

Fungal prophylaxis is generally initiated posttransplant with an imidazole and/or nebulized, inhaled amphotericin B. Therapeutic drug monitoring analysis identified voriconazole levels were often undetectable in treated CF lung transplant patients, supporting the use of antifungal drug combinations, until steady-state levels can be achieved with higher doses.[88] Voriconazole acted as a metabolic inhibitor of tacrolimus, so large changes in voriconazole concentration affected the magnitude of this drug–drug interaction requiring tacrolimus dose adjustments. More recently, voriconazole prophylaxis after lung transplantation was associated with a higher incidence of hepatotoxicity but similar clinical effectiveness when compared with itraconazole (this study included nonbronchiectatic lung transplant recipients).[89]

For the first 15 years of lung transplantation, a significant cause of early death was airway dehiscence.[90] Due to advancements in lung preservation and surgical technique along with improvements in candidate selection, postoperative care, immunosuppression, and antibiotic/antifungal therapy, the prevalence of airway complications has significantly decreased.[91,92] In a recent study of 255 patients who underwent lung transplant, the highest rate of airway complications occurred in the CF recipients (12/31 complications).[93] The higher risk for these complications in CF may be related to the chronic pathogens harbored in their airways that are opportunistic and may infect ischemic areas at the bronchial anastomosis.

The major causes of posttransplant morbidity and mortality in patients with bronchiectasis are infection and allograft rejection. After lung transplant for suppurative lung disease, the pathogens isolated from respiratory secretions prior to transplant are usually the cause of posttransplant bacterial respiratory infections, especially in CF.[81] The paranasal sinuses in CF patients frequently harbor the same pathogens as seen in the lower airways, so these organisms can infect the lower respiratory tract after lung transplant. Endoscopic sinus surgery is frequently performed, but there are no convincing data that it affects outcomes after lung transplantation in CF.

Persistent allograft colonization with *Pseudomonas* increased the prevalence of BOS after lung transplant, especially in CF patients.[94–96] In a very interesting study by Bonvillain et al,[95] normal lungs implanted into CF patients had significantly higher susceptibility to *Pseudomonas* infections than those lungs placed into patients with other transplant indications, which suggests that defective systemic innate immunity contributes to CF lung pathogenesis.

A significant proportion of these posttransplant CF patients demonstrated immediate eradication of the pathogen in the lower respiratory tract samples upon later follow-up, which may have protected against the development of BOS. Treatment of BOS has included alteration of immunosuppressant therapy,[97] but the prognosis remains poor. Azithromycin, which has immunomodulatory properties, has been identified as a potential therapeutic agent that stabilizes or possibly reverses pulmonary function decline in BOS.[98–100] Gottlieb et al[101] found that the majority of patients who had improvement in airflow limitation with azithromycin therapy improved after 3 months of treatment, and bronchoalveolar lavage (BAL) neutrophilia appeared to have predictive value. The authors speculated that a beneficial effect on GERD (enhanced bowel motility and clearance of gastric contents) may be a mechanism of action. In a more recent study, lung transplant recipients receiving azithromycin had significantly less GER and bile acid aspiration.[102] The investigators measured acid and weakly acidic GER with 24-hour pH-impedance monitoring in 47 lung transplant recipients, with 12 of them receiving azithromycin. Gastric aspiration was assessed in a separate group of 30 lung transplant recipients before and after azithromycin by measurements of pepsin and bile acid in BAL fluid. Patients on azithromycin therapy had a significantly

lower total number of reflux events, number of acid reflux events, esophageal acid exposure, bolus exposure, and proximal extent of reflux while azithromycin reduced the concentration of bile acids in BAL fluid without affecting levels of pepsin.

OUTCOMES

Dramatic improvement in pulmonary function can occur after lung transplant in CF patients, with the mean FEV_1 increasing from 20% to 80% predicted and the mean forced vital capacity (FVC) increasing from 38% to 82% predicted in 44 CF patients who underwent double lung transplantation over a 3.5-year period.[103] Spahr et al[82] demonstrated a mean increase in FEV_1 from 24.8% prior to transplant to 85.4% at 1-year follow-up. Following recovery from transplantation, patients should be able to perform activities of daily living without limitations if significantly pulmonary complications are not present. However, maximum oxygen consumption on formal exercise testing may remain limited despite improved physiological parameters. Williams et al[104] reported that VO_2max (maximal oxygen uptake at peak exercise) was 46% of predicted for single lung transplant recipients and 50% of predicted for double lung transplant recipients. Additionally, Levy et al[105] demonstrated that transplant recipients reached maximum oxygen uptakes in the range of 40% to 60% of predicted values at peak exercise.

Egan et al[106] reported long-term survival over a period of 10 years with 131 lung transplant procedures for 123 patients with CF (114 bilateral sequential lung transplants and nine with bilateral lower lobe transplants with living donors), with three patients undergoing retransplant for acute graft failure and five having late retransplant for BOS. The survival rates were 81% at 1 year, 59% at 5 years, and 38% at 10 years. Survival outcomes are the highest in the CF population compared with other patient populations that undergo lung transplantation.[12] Beirne et al[38] reported that survival and pulmonary function after lung transplantation for non-CF bronchiectasis were similar to those for recipients with CF in their single-center experience.

Although the burden of care that ongoing posttransplant therapies place on these lung transplant recipients is considerable, QoL is improved despite the need for posttransplant surveillance and complications of chronic immunosuppressant therapy. Vermeulen et al[107] assessed the health-related QoL in patients transplanted for CF compared with those transplanted for other reasons. The CF patients were more likely to work or attend school prior to transplantation and also reported greater mobility and energy. Both the CF and non-CF groups reported significant improvement in health-related QoL up to 31 months after lung transplantation, and significant improvements in QoL appear to be sustained for at least 1 to 3 years after transplant.[108] Lung transplant recipients generally were satisfied with their decision to have undergone transplantation. Despite the side effects of immunosuppression, transplant recipients report a highly satisfying QoL with regard to physical and emotional well-being and social and sexual function.[109] A total of 76% of lung transplant patients were highly satisfied with their transplant outcome, and 92% would undergo the procedure again. Recipients with CF constituted the group that was most satisfied with their posttransplant QoL.

SUMMARY

Lung transplant can be successfully performed on patients with advanced bronchiectatic lung disease with subsequent good posttransplant QoL and long-term outcome. Despite the presence of chronic lower respiratory tract infection with bacterial pathogens in these patients pretransplant, posttransplant infections do not generally have significant impact on survival, but infection with antibiotic-resistant bacteria may complicate posttransplant management. Although benefit of lung transplantation for young children with CF has been somewhat controversial, lung transplantation can clearly benefit older children and adults with advanced lung disease due to bronchiectasis.

KEY POINTS

- Identification of the cause of bronchiectasis should be sought in all patients who appear to have non-CF bronchiectasis.
- Adequate maintenance therapies and optimal management of disease exacerbations are key to successful management of patients with CF and non-CF bronchitis.
- Comorbidities of advanced bronchiectasis should be detected and treated.
- Patients with advanced lung disease and declining lung function should be considered for lung transplant referral.
- Patients with CF and non-CF bronchiectasis have generally good outcomes following lung transplantation.
- Management of infection is a key issue both before and after lung transplantation.

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