

# The Patient Who Has Undergone Lung Transplantation: Implications for Respiratory Care

Stephanie M Levine MD and Luis F Angel MD

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**Lung transplantation is now performed in patients with end-stage pulmonary parenchymal or vascular lung disease. The process of evaluating a patient for transplantation, managing the patient during the peri-operative period, and caring for the patient following transplantation is complex. Lung-transplant recipients are prone to unique complications of lung transplantation, as well as general complications of an immunosuppressed host. This article reviews the indications for, expected outcomes of, and management of complications that can develop following lung transplantation. Respiratory therapists play an instrumental role in assisting in the management of this group of patients in the pretransplant and post-transplant periods, and in their long-term management. Key words: lung transplantation, postoperative, rejection, obliterative bronchiolitis, post-operative management, patient assessment. [Respir Care 2006;51(4):392–402. © 2006 Daedalus Enterprises]**

## Introduction

Lung transplantation (LT) has become an accepted therapeutic option for patients with end-stage pulmonary paren-

chymal or vascular disease over the past 2 decades. Historically, the procedure was infrequently performed and encountered numerous problems. The first human LT was performed by Hardy in 1963, but the patient survived only 18 days.<sup>1</sup> From 1963 until 1980, nearly 40 more LTs were attempted, but the longest survival was only 10 months.<sup>2,3</sup> The primary reason these early LT attempts were unsuccessful was the development of rejection or infection in the transplant recipients.<sup>2,3</sup>

Improvements in surgical techniques, immunosuppressive therapy (initially with the discovery<sup>4</sup> of cyclosporine A), and standardization of selection criteria for LT recipients have

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Stephanie M Levine MD is affiliated with the Division of Pulmonary and Critical Care Medicine, University of Texas Health Science Center, and Audie L Murphy Memorial Veterans Hospital, San Antonio, Texas. Luis F Angel MD is affiliated with the Division of Pulmonary and Critical Care Medicine and the Division of Cardiothoracic Surgery, University of Texas Health Science Center, San Antonio, Texas.

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Correspondence: Stephanie M Levine MD, Division of Pulmonary and

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Critical Care Medicine, University of Texas Health Science Center, 7703 Floyd Curl Drive, San Antonio TX 78229. E-mail: levines@uthscsa.edu.

Table 1. Major Indications for Lung Transplantation by Procedure

Single-Lung Transplantation
Chronic obstructive lung disease
Pulmonary fibrosis
Alpha-1 antitrypsin deficiency
Sarcoidosis
Other
Bilateral Lung Transplantation
Cystic fibrosis
Chronic obstructive lung disease
Pulmonary fibrosis
Pulmonary hypertension
Bronchiectasis
Other

revolutionized the field. In 2003 over 1,700 LTs were performed worldwide, as reported to the International Society for Heart and Lung Transplantation.<sup>5</sup> This article will briefly review the available surgical procedures and indications for LT, concentrating primarily on the post-LT recipient and the myriad of complications that commonly occur in these patients.

### Indications for Lung Transplantation

Restrictive parenchymal lung disease is a common indication for single-lung transplantation (SLT), and SLTs have been performed for idiopathic and familial pulmonary fibrosis, drug- or toxin-induced lung disease, occupational lung disease, sarcoidosis, limited scleroderma, and other disorders resulting in end-stage fibrotic lung disease. SLTs are also performed in patients with chronic obstructive pulmonary disease (COPD) and in patients with alpha-1 antitrypsin deficiency. Currently, COPD is the most common indication for SLT reported to the registry of the International Society for Heart and Lung Transplantation, at 53%.<sup>5</sup> SLT has also been performed successfully in patients with pulmonary vascular disease, although in general bilateral lung transplantation (BLT) is preferred for this indication.

In patients with suppurative pulmonary lung disease, such as cystic fibrosis or idiopathic bronchiectasis, BLT is required because of potential infection from the remaining native lung. Some transplant centers perform BLT for severe obstructive lung disease in young patients with emphysema because of a longer post-transplant life expectancy. Patients receiving SLT for this disease are often difficult to manage in the intraoperative and postoperative periods, as they can develop substantial ventilation-perfusion mismatch during times of graft dysfunction. For this reason, most centers also prefer BLT for pulmonary hypertension, in an attempt to distribute blood flow equally to both lungs. Table 1 summarizes lung-transplantation procedures by disease state.

### Evaluation

Those patients being considered for LT undergo a series of tests for further assessment. These studies include pulmonary function tests (PFTs, including lung volumes, spirometry, and diffusing capacity), and a measure of exercise performance, usually a 6-min-walk test. Cardiac evaluation includes an electrocardiogram and an echocardiogram, in addition to some functional cardiac study such as dobutamine echocardiography and/or coronary angiography in patients over the age of 40. A high-resolution computed tomogram (CT) is usually obtained to look for bronchiectasis, which could indicate the necessity for a bilateral procedure, or to look for focal nodules not apparent on plain radiograph. Renal and liver function are assessed by 24-hour creatinine clearance and liver function tests, respectively. A complete blood count and viral serologies are also obtained.

### Outcomes

Following transplantation, lung function gradually improves and reaches a plateau by 36 months following surgery. SLT for obstructive lung disease results in residual mild-to-moderate obstructive pulmonary dysfunction secondary to the remaining native lung.<sup>6</sup> An SLT recipient who has underlying restrictive lung disease will have a residual mild restrictive defect.<sup>7-10</sup> SLT recipients with pulmonary vascular disease maintain their normal pulmonary function and develop normal hemodynamics following transplantation.<sup>11</sup> BLT performed for any indication results in improved spirometry values.<sup>12,13</sup> All of the different LT procedures result in normal gas exchange following transplantation. Exercise testing uniformly shows reduced maximum exercise capacities, with no evidence of ventilatory limitation or arterial oxygen desaturation. There is no significant difference in exercise capacity between patients who undergo SLT versus BLT, despite the differences in spirometry values with SLT.<sup>7-9,14</sup> Despite the reduced exercise capacities, all stable patients are able to carry out activities of daily living without compromise.

One-year, 2-year, 3-year, and 5-year survival rates of LT recipients are 76%, 68%, 60%, and 49%, respectively,<sup>5</sup> which is lower than those achieved with other solid-organ transplantations. Mortality in the early postoperative period has been caused primarily by technical complications and primary graft failure. Mortality after the perioperative period (beyond 30 d) and up to 1 year is primarily due to infection. Mortality beyond the first year has been primarily related to bronchiolitis obliterans, the sine qua non of chronic rejection.

Chest radiographs following SLT for COPD or pulmonary fibrosis reflect the transplanted lung in one hemithorax and the native remaining lung in the contralateral hemithorax. In the case of COPD, the remaining hyperinflated native lung has the larger volume and sometimes radiographically ap-

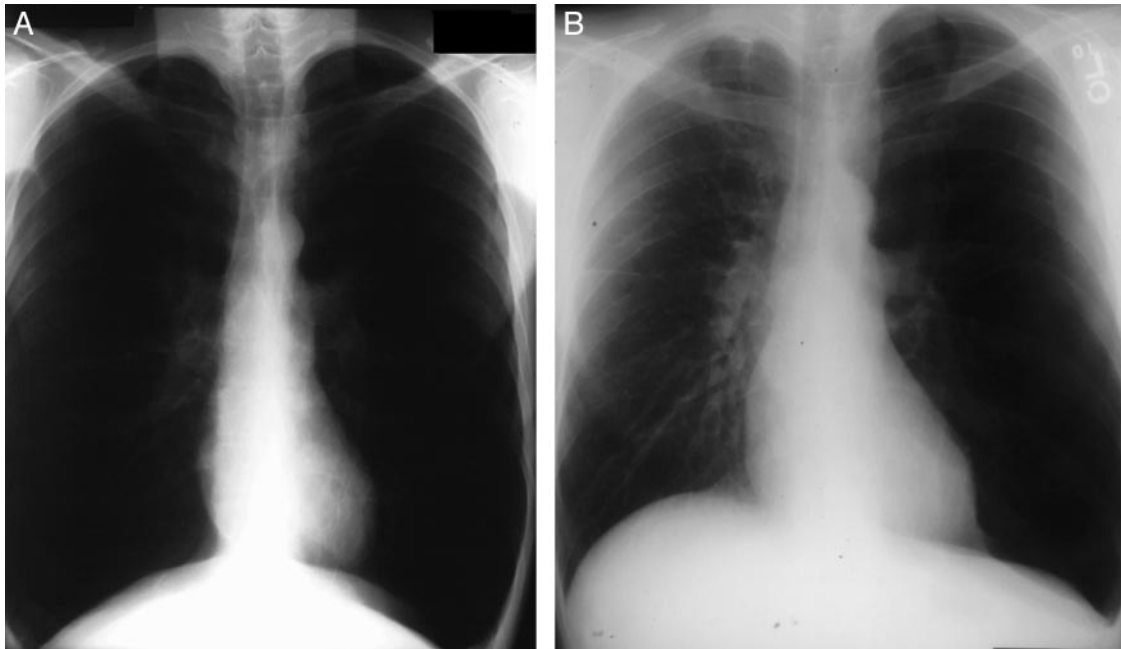


Fig. 1. Posteroanterior chest radiograph of a patient with emphysema before (left) and after (right) a right-side single-lung transplant procedure.

pears to compress the transplanted lung (Fig. 1). In the case of SLT for idiopathic pulmonary fibrosis, the transplanted lung (in this case on the left) is the larger-volume lung, and the native fibrotic lung has less volume (Fig. 2).

Quality-of-life issues are a relatively recent subject of research in LT. Several small studies have shown improvement in overall and health-related quality of life.<sup>15-18</sup> The large majority of patients have expressed satisfaction with the transplant decision. Even if survival advantage is in question, the improvement in quality of life is worth the sacrifice to many patients.

#### Management After the Postoperative Period

After discharge, follow-up is performed in the outpatient clinic. An example follow-up schedule would be weekly for the first 2 months, biweekly for the next month, and monthly thereafter. After 3 months of uncomplicated post-transplant observation, patients often return home and resume follow-up with their referring pulmonologists.

Weekly studies include measurement of cyclosporine or tacrolimus level, a complete blood count to monitor the leukocyte count on azathioprine or mycophenolate mofetil,

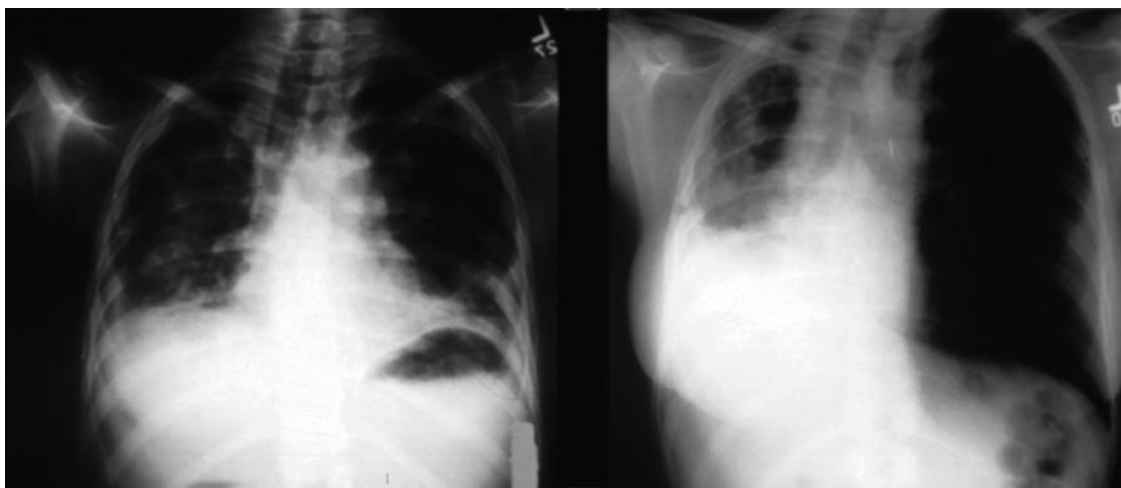


Fig. 2. Posteroanterior chest radiograph of a patient with interstitial lung disease before (left) and after (right) a left-side single-lung transplant procedure.

blood chemistries to follow creatinine while on cyclosporine or tacrolimus and to follow liver-function tests, a chest radiograph, routine spirometry, and exercise oximetry. In addition, patients bring in their home spirometry measurements at each visit. Some institutions perform surveillance bronchoscopy on a routine schedule, while other institutions reserve this procedure for clinical deterioration.

The most efficient and effective way to monitor for early rejection, infection, or anastomotic complications remains controversial. Chest radiographs have been shown to be neither specific nor sensitive for early detection of infection or rejection.<sup>19–22</sup> Close monitoring of pulmonary function has also been studied as a way of detecting graft complications.<sup>23,24</sup> At most transplant centers, patients are given home spirometers and instructed to document their forced expiratory flow in the middle half of the forced vital capacity (FEF<sub>25–75</sub>), forced expiratory volume in the first second, and forced vital capacity twice a day. The training for home spirometry is usually conducted by the transplant respiratory therapist. The patient is instructed to notify his or her local physician or the transplant center if these values decline by 10–15% on 2 subsequent measurements. Although PFTs cannot distinguish between rejection and infection, PFT does have 84% specificity for detecting complications in the lung graft.<sup>20</sup>

Surveillance bronchoscopy has become a controversial issue in LT. Reports suggest that surveillance bronchoscopy may allow the early detection of asymptomatic complications such as acute rejection and could thus reduce future development of obliterative bronchiolitis (OB). A study that compared transplant recipients who had undergone surveillance bronchoscopy as historical controls to transplant recipients who did not undergo surveillance bronchoscopy did not find a difference in bronchiolitis obliterans syndrome or survival.<sup>25</sup> However, a recent large survey of 50 transplant centers reported that 69% continue to perform surveillance bronchoscopy on a regular basis.<sup>26</sup>

## Complications Following Lung Transplantation

### Postoperative Complications

Perhaps the most important problem in the LT postoperative period is the development of primary graft dysfunction, also termed the pulmonary reimplantation response or primary graft failure.<sup>27</sup> It is estimated that up to 80% of patients experience some degree of reimplantation injury,<sup>28,29</sup> and up to 15% of cases can be severe.<sup>30</sup> To varying degrees, primary graft dysfunction can persist for hours to days following LT. Clinically, primary graft dysfunction is characterized by new radiographic alveolar and/or interstitial infiltrates, a decrease in pulmonary compliance, increased pulmonary vascular resistance, and disrupted gas exchange. Radiographic findings in these



Fig. 3. Anteroposterior portable chest radiograph of a 50-year-old woman with chronic obstructive pulmonary disease, taken 6 hours after a right-side single-lung transplant procedure. Note the alveolar infiltrates caused by primary graft dysfunction.

patients included a perihilar haze, patchy alveolar consolidations and dense perihilar and basilar alveolar consolidations with air bronchograms (Fig. 3). Pathology results from biopsy specimens, autopsies, or lung explants removed during retransplantation reveal diffuse alveolar damage. Primary graft dysfunction usually worsens or stabilizes over the subsequent 2–4 days and then begins to resolve. Severe primary graft dysfunction usually leads to compromised short-term outcomes, including duration of mechanical ventilation, length of stay, short-term survival, and costs. The long-term outcomes in survivors, such as pulmonary function and incidence of bronchiolitis obliterans, have differed among studies, with some reporting compromise and others without long-term adverse effects.<sup>31</sup>

Although the mechanism of primary graft dysfunction has not been completely delineated, several contributing factors have been postulated, including the disruption of lymphatics, bronchial vasculature, and/or nerves, as well as lung injury occurring either during preservation of the graft or following reperfusion. Postulated recipient risk factors include pulmonary hypertension and cardiopulmonary bypass, among others.<sup>32,33</sup>

In general, primary graft dysfunction develops in the immediate postoperative period, but can develop 24–72 hours following transplantation, whereas rejection and infection are more common after the first 24 hours. However, since the timing of these disorders may differ, distinguishing between them can be difficult. Primary graft dysfunction is managed supportively with diuretics and mechanical ventilation, often using a lung-protective ventilation strategy.<sup>34</sup> There are several reports of the use of inhaled nitric oxide,<sup>35–37</sup> extracorporeal membrane oxygenation, and artificial surfactant replacement for severe early graft dysfunction.<sup>38</sup> High-frequency oscillatory ventilation and independent lung

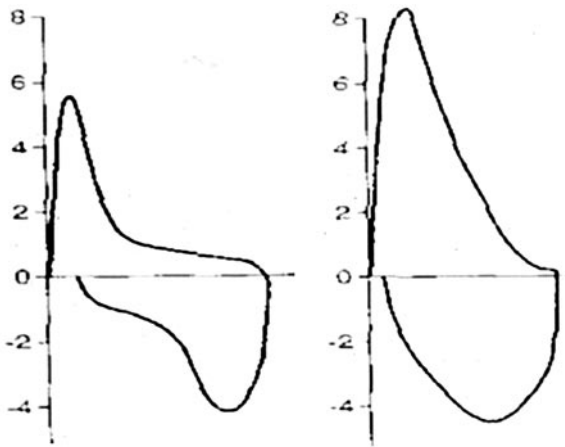


Fig. 4. Flow-volume loops from a single-lung transplant recipient with a bronchial stenosis before (left) and after (right) bronchial stent placement.

ventilation have also been used in some cases. Retransplantation has also been performed.

### Airway Complications

Airway problems, which were an important cause of morbidity and mortality following early LT attempts, developed in 20–50% of LT recipients.<sup>39–42</sup> More recently, airway complications have had a prevalence of 10–20%, with a low mortality.<sup>43–45</sup> Airway complications can be divided into early and late time periods. Early complications typically develop in the first 1–2 months following transplantation and are characterized by anastomotic infection and/or partial or complete anastomotic dehiscence. Subsequently, anastomotic strictures and/or bronchomala-



Fig. 5. Bronchoscopic view of the left main bronchial anastomosis, with an *Aspergillus* infection.

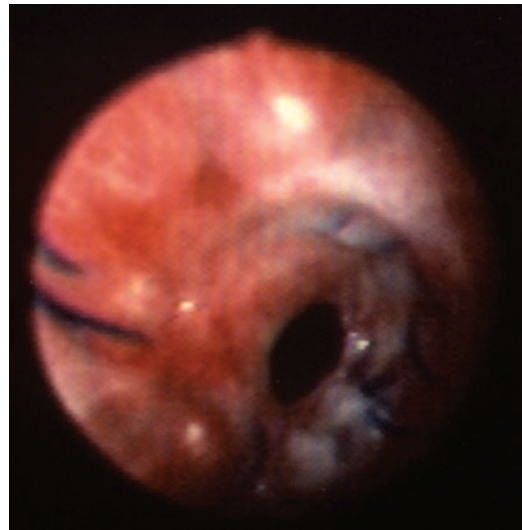


Fig. 6. Bronchoscopic view of the left main bronchial anastomosis 6 weeks following treatment for *Aspergillus* tracheobronchitis. Note the stenosis at the site of the anastomosis.

cia can develop, which substantially compromise the function of the transplanted lung or lungs. Several theoretical causes of airway complications have been postulated, including ischemia at the site of the anastomosis, infection of the anastomosis, poor organ preservation, pneumonia, graft rejection, early corticosteroid administration, and an excessively long donor bronchus.

Clinically, bronchial stenosis can present with cough, shortness of breath, dyspnea on exertion, and worsening obstruction on PFT. A characteristic flow-volume loop with an inspiratory and expiratory concave pattern has been noted (Fig. 4).<sup>46</sup> Radiographically, bronchial strictures may be seen on posteroanterior chest radiograph and can be clearly visualized on CT and/or the definitive test, bronchoscopy. Partial or complete bronchial dehiscence can present with mediastinal emphysema on chest radiograph or air adjacent to the bronchial anastomosis on CT.<sup>22</sup>

Anastomotic complications can be easily diagnosed on bronchoscopy (Fig. 5). Anastomotic ischemia warrants close bronchoscopic observation. If an anastomotic infection is diagnosed, most commonly with *Staphylococcus aureus*, *Pseudomonas aeruginosa*, or *Aspergillus* species, appropriate antibiotics should be initiated.<sup>47</sup> Anastomotic strictures (Fig. 6) should be treated with balloon dilation, wire or silastic stent placement (Fig. 7), laser, or surgery.<sup>45,48</sup> Partial anastomotic dehiscence is managed conservatively. Complete dehiscence requires surgical revision of the anastomosis or retransplantation.

### Acute Rejection

Acute rejection is a common immunologic response that affects the majority of LT recipients in the first few months

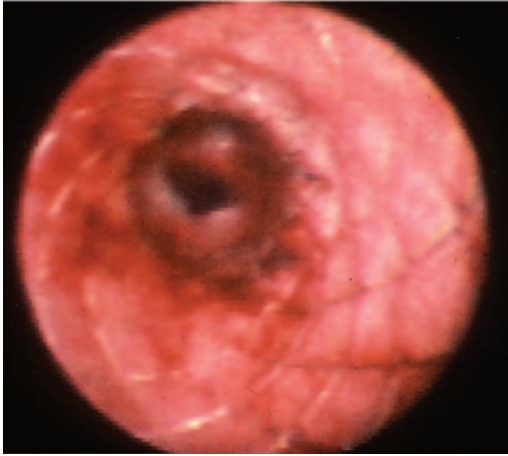


Fig. 7. Bronchoscopic view following wire-mesh stent placement for the bronchial stenosis seen in Fig. 6.

following transplantation. Acute rejection is usually not seen as frequently after the first year post-transplantation.<sup>49</sup> The clinical features of acute rejection include cough, dyspnea, fever, and sometimes crackles or wheezes on lung examination. The chest radiograph is usually abnormal during rejection in the first month after transplantation, but is abnormal in only one fourth of cases after the first month.<sup>21,50</sup> The most common radiographic pattern has been a perihilar or lower-lobe infiltrate, often associated with a small pleural effusion.<sup>51</sup>

Hypoxemia and deterioration in pulmonary-function studies frequently occur in the setting of acute rejection. Thus, a decline of  $\geq 10\%$  in forced vital capacity or FEV<sub>1</sub> and a 10–15% decline in FEF<sub>25–75</sub> are important changes and may signal either acute rejection or infection or some other graft complication.<sup>20</sup>

Clinical criteria alone cannot differentiate acute rejection from infection. Transbronchial biopsy with bronchoalveolar lavage has emerged as the primary procedure in distinguishing rejection from infection. The reported sensitivity for diagnosing rejection has ranged from 70% to 95%, and the specificity from 90% to 100%.<sup>52–54</sup> Histologically, acute rejection is characterized by perivascular mononuclear infiltrates and may also have airway involvement, lymphocytic bronchitis, or bronchiolitis.<sup>55</sup>

There is a histologic grading system for acute pulmonary rejection, initially defined in 1990 and revised in 1996.<sup>55</sup> The standard therapy for acute pulmonary rejection is high-dose corticosteroids, which usually leads to a dramatic improvement in the patient's condition within 24 hours if the diagnosis is correct. The maintenance immunosuppressive regimen should also be optimized, and the prednisone escalated to 1 mg/kg/d, with a taper over several weeks. Conversion from a cyclosporine-based to a tacrolimus-based regimen may also result in improvement (decreased incidence and severity) of persistent or recur-

rent acute rejection.<sup>56</sup> Lympholytic therapy, methotrexate, photophoresis, total lymphoid irradiation, and aerosolized cyclosporine have also been used for treatment of recurrent or persistent acute rejection.<sup>56–60</sup>

### Obliterative Bronchiolitis

OB following transplantation is defined clinically by an obstructive pulmonary-function defect and histologically by obliteration of terminal bronchioles (bronchiolitis obliterans). Many large transplant centers report a 45–50% incidence of OB in LT recipients who survive 5 years after transplant.<sup>5</sup> OB remains a major problem in LT and is the leading causes of late mortality.<sup>61</sup>

Several possible risk factors for OB have been proposed, although the etiology remains unclear. Proposed risk factors include uncontrolled acute rejection,<sup>62–64</sup> cytomegalovirus pneumonia,<sup>65</sup> human leukocyte antigen A (HLA-A) mismatches, total HLA mismatches, absence of donor antigen-specific hyporeactivity,<sup>64</sup> bronchiolitis obliterans with organizing pneumonia, and lymphocytic bronchiolitis.<sup>66,67</sup> Acute rejection has been consistently identified as the most important risk factor for bronchiolitis obliterans syndrome.<sup>68–72</sup>

Clinically, OB has been reported at any time following the third month after transplantation, but the typical onset is 16–20 months after surgery.<sup>70,73</sup> The onset of OB may be heralded by an upper-respiratory-tract infection and can be mistakenly treated as such. Other patients present without clinical symptoms but with a gradual obstructive dysfunction on PFT.<sup>74</sup> Typically, chest radiographs are not helpful in diagnosing OB, because in most patients the radiograph will be unchanged from the baseline post-transplant radiograph.<sup>74</sup> Some investigators have described central bronchiectasis as a radiographic finding that suggests a diagnosis of OB.<sup>75</sup> High-resolution CT in OB may reveal peripheral bronchiectasis, patchy consolidation, decreased peripheral vascular markings, air trapping on expiratory views, and bronchial dilation, which may aid in the early diagnosis of OB.<sup>76–79</sup>

Transbronchial biopsy is used in the evaluation of suspected OB. In addition to occasionally revealing histologic changes of OB, bronchoscopy is important in excluding other possible diagnoses (such as acute rejection, infection, or airway complications) as contributing causes of deteriorating pulmonary function. Unfortunately, it may be difficult to obtain diagnostic specimens of the terminal bronchioles via transbronchial biopsy. The reported sensitivity of transbronchial biopsy for detecting OB has ranged from 15% to 87%.<sup>50,68,80–83</sup> OB is often a diagnosis of exclusion in a patient who presents with progressive obstruction on PFT and with an otherwise normal transbronchial biopsy.

Because of the variability in detecting OB via transbronchial biopsy, the International Society for Heart and Lung Transplantation has established a bronchiolitis obliterans syndrome staging system.<sup>84</sup> This staging is based on the reduc-

Table 2. 2001 Clinical Staging System for Obliterative Bronchiolitis

Stage*	Presence/Extent of OB	FEV <sub>1</sub>
BOS 0	No OB	FEV <sub>1</sub> > 90% of baseline, and FEF <sub>25-75</sub> > 75% of baseline
BOS 0-p	Potential OB	FEV <sub>1</sub> 81-90% of baseline, and/or FEF <sub>25-75</sub> ≤ 75% of baseline
BOS 1	Mild OB	FEV <sub>1</sub> 66-80% of baseline
BOS 2	Moderate OB	FEV <sub>1</sub> 51-65% of baseline
BOS 3	Severe OB	FEV <sub>1</sub> ≤ 50% of baseline

\*Each stage is subdivided into *a* and *b*, where *a* is without histologic documentation of OB, and *b* is with histologic documentation of OB.

OB = obliterative bronchiolitis

BOS = bronchiolitis obliterans syndrome

FEV<sub>1</sub> = forced expiratory volume in the first second

FEF<sub>25-75</sub> = forced expiratory flow in the middle half of the forced vital capacity

(Adapted from Reference 72.)

tion in FEV<sub>1</sub> and mid-flow, in comparison to post-transplant baseline values, with or without pathology documentation of OB (Table 2), and implies that other causes of the physiologic changes (such as acute rejection, airway complications, and infection) have been excluded with bronchoscopy.<sup>72</sup>

If OB has been diagnosed histologically or clinically by exclusion of alternative diagnoses, treatment is begun with high-dose methylprednisolone, followed by a tapering course of oral corticosteroids. Lympholytic agents such as anti-lymphocyte globulin or muromonab-CD3 (Orthoclone OKT or OKT3) can be considered if there is no clinical response to steroid treatment. Therapy may stabilize the pulmonary function but uncommonly results in substantial improvement.<sup>85</sup> Mycophenolate mofetil and tacrolimus have also been associated with stabilization of pulmonary function when used as salvage treatment for bronchiolitis obliterans syndrome.<sup>86-88</sup> Methotrexate, photophoresis, total lymphoid irradiation, inhaled cyclosporine, and newer immunosuppressive agents have been used in refractory cases of OB.<sup>89</sup>

### Infectious Complications

Infection is a leading cause of morbidity and mortality in LT recipients.<sup>90,91</sup> The lung's defense mechanisms are dramatically diminished because neither the nerve supply nor the lymphatic drainage of the transplanted lung are reestablished. Mucosal ischemia impairs mucociliary clearance, and the anastomosis impairs the movement of mucus up the trachea. These factors, along with immunosuppression, explain why 30-80% of transplant recipients develop infections, particularly pneumonia, within the early months following transplantation.<sup>90-92</sup>

One of the most common life-threatening infections in the early postoperative period is bacterial pneumonia. The risk of pneumonia in the first 2 postoperative weeks has been reported to be as high as 35%.<sup>93</sup> *Pseudomonas aeruginosa* and *Staphylococcus* species have been the predominant pathogens. With the use of broad-spectrum antibiotic prophylaxis (usually an antipseudomonal cephalosporin

and clindamycin) and routine culturing of the tracheas of the donor and recipient at the time of surgery, the incidence of bacterial pneumonia has been reduced to around 10%. If the cultures remain negative, prophylactic antibiotics are discontinued after 3-4 days.

Atypical pneumonias, including *Legionella*, mycobacteria, and *Nocardia*, are uncommon in the first month, but can occur in 2-9% of lung and heart-lung transplant recipients.<sup>94</sup> In transplant centers where trimethoprim-sulfamethoxazole prophylaxis is routinely used during the first year after transplant and reinitiated when immunosuppression is augmented, the incidence of pneumocystis pneumonia is < 1%.<sup>94-96</sup> Nevertheless, LT recipients have a 5-fold higher prevalence of pneumocystis pneumonia than do comparably immunosuppressed recipients of cardiac allografts, and pneumocystis pneumonia must be considered in the differential diagnosis of pneumonia in this population.<sup>96</sup>

Most opportunistic infections occur 1-6 months after transplantation. Sustained immunosuppression leads to decreased cell-mediated immunity, which predisposes the patient to infection by opportunistic organisms, including *Aspergillus*, *Mycobacterium*, *Nocardia*, and geographically endemic fungi. During this time period, viral infections are a major cause of mortality and morbidity. *Cytomegalovirus*, which is a herpes virus, accounts for the majority of the viral infections in these patients.

*Cytomegalovirus* is the most common cause of infections 30-150 days after LT.<sup>93</sup> The overall prevalence of cytomegalovirus illness (infection or disease) in LT recipients has been approximately 50%.<sup>61</sup> The risk of developing cytomegalovirus disease depends on the serologic status of the donor and the recipient, as well as on the use of high-intensity immunosuppressive therapy. Cytomegalovirus-positive recipients develop cytomegalovirus disease approximately 25-35% of the time, whereas cytomegalovirus-negative recipients have an 85% chance of developing cytomegalovirus disease when implanted with a cytomegalovirus-positive lung.<sup>97</sup>

*Cytomegalovirus* causes a wide spectrum of diseases, ranging from asymptomatic infection (shedding of virus in urine or bronchoalveolar secretions) to widespread dissemination. Cytomegalovirus infection in transplant patients is characterized by active replication and shedding of virus, which can be associated with unexplained fever or constitutional symptoms, as well as laboratory abnormalities, including mild atypical lymphocytosis, leukopenia, or thrombocytopenia. Cytomegalovirus disease is established by cytologic or histologic changes in cell preparations or tissue. Although cytomegalovirus disease can also be manifested by hepatitis, gastroenteritis, or colitis, cytomegalovirus pneumonia is the most common presentation after LT.

Cytomegalovirus pneumonia typically presents insidiously, with nonproductive cough, fever, malaise, hypoxemia, and a mild interstitial or alveolar infiltrate. Sputum smears and cultures are rarely diagnostic for cytomegalovirus pneumonia. Fiberoptic bronchoscopy with transbronchial biopsy and bronchoalveolar lavage can diagnose 60–90% of patients with cytomegalovirus pneumonia.<sup>92,94</sup> The microscopic hallmark of cytomegalovirus infection is the large (cytomegalic) 250-nm cell, which contains a large central basophilic intranuclear inclusion, referred to as an “owl’s eye” because it is separated from the nuclear membrane by a halo. A presumptive diagnosis is often made on the basis of a positive polymerase-chain-reaction blood test in a compatible clinical setting, after other causes have been excluded. Ganciclovir, an acrylic guanine analogue, is currently the mainstay of therapy for invasive cytomegalovirus disease. Cytomegalovirus-specific immunoglobulin G, in combination with ganciclovir, may also be used.

Although there is no consensus about the optimal regimen for preventing cytomegalovirus disease, prophylaxis against cytomegalovirus infection has become a major strategy in most transplant centers. The easiest way to reduce cytomegalovirus infections is to match cytomegalovirus-negative recipients with cytomegalovirus-negative donors whenever possible, but the severe limitation in available donated grafts make this strategy impractical. Limited studies suggest that cytomegalovirus hyperimmune globulin may prevent or ameliorate serious cytomegalovirus infections in high-risk patients after renal, liver, or heart transplantation.<sup>98,99</sup> A preemptive strategy is attractive because it treats only those patients at higher risk for developing cytomegalovirus disease. Surveillance cultures using quantitative sensitive assays, such as cytomegalovirus antigenemia or polymerase chain reaction, offer important advantages over previous methods.

The overall incidence of invasive fungal infections with lung or heart-lung transplantation ranges from 10% to 22%.<sup>100,101</sup> Fungal infections are more common in LT recipients than in those who receive other solid-organ transplants. Most fungal infections are caused by *Candida* or *Aspergillus* species, and over 80% of fungal infections occur within the

first 2 months.<sup>100</sup> The overall mortality of fungal infections in LT recipients has been reported to be as high as 40%.<sup>100,101</sup>

*Aspergillus* species (*A. fumigatus*, *A. flavus*, *A. terreus*, and *A. niger*) may be present as an indolent progressive pneumonia or as an acute fulminant infection that rapidly disseminates. *Aspergillus* exhibits a propensity to invade blood vessels and may present as an infarct or with hemoptysis. The radiographic features of pulmonary aspergillosis include focal lobar infiltrates, patchy bronchopneumonic infiltrates, single or multiple nodules with or without cavitation, thin-walled cavities, and opacification of the entire lung graft. High-resolution CT may reveal a halo sign, which is believed to be pathognomonic for invasive aspergillosis.<sup>101</sup> Prophylaxis with azoles, such as itraconazole and, more recently, voriconazole, or inhaled amphotericin has shown promise in decreasing the incidence of aspergillus infections.<sup>102</sup>

Definitive diagnosis of invasive aspergillosis requires identification of organisms within tissue. Even with documented cases of invasive aspergillosis, cultures are positive in < 50% of cases.<sup>92,103</sup> Another form of aspergillus infection is aspergillus tracheobronchitis.<sup>47,104</sup> These patients develop ulcerative tracheobronchitis, which usually starts distal to the anastomosis and may result in progressive narrowing of the airway.

Improved survival has been achieved with the early initiation of itraconazole and/or high-dose amphotericin (1 mg/kg/d) or inhaled amphotericin, and the reduction of immunosuppressive therapy.<sup>105</sup> Surgical resection and medical therapy may be required to maximize cure rates in patients with invasive aspergillosis, especially those with persistent signs of infection or necrotic tissue.<sup>103</sup> Oral itraconazole (400 mg/d) compares favorably with amphotericin in uncontrolled studies.<sup>47,106</sup> Newer azoles, such as voriconazole, are also of use in the LT population. A lipid formulation of amphotericin B should be considered in the management of invasive fungal infections in patients who are intolerant of conventional amphotericin B and in patients with progressive fungal infection despite therapy with amphotericin-deoxycholate.<sup>101</sup>

Less common causes of fungal infections in LT recipients include *Cryptococcus neoformans* and the dimorphic fungi (*Coccidioides*, *Histoplasma*, and *Blastomyces*). Amphotericin B and/or newer azole agents are the initial choices for therapy for serious infections with the invasive mycoses. The dose, duration of therapy, and alternative therapy depend on the organism.<sup>105</sup>

Miscellaneous post LT complications—including lymphoproliferative disorders, gastroesophageal reflux, pulmonary embolism, and complications with immunosuppression—can also develop but are beyond the scope of this review.

## Summary

The field of LT has seen many advances over the past 20 years. One can appreciate that respiratory therapists

play an important role in the care of the LT patient, throughout all periods of management: in the preoperative period, in the performance of PFT and exercise testing; in the perioperative period, assisting with the management of newer ventilation strategies for management of primary graft failure; and in the postoperative period, in helping with prescriptions for home spirometry, PFT, and, at many centers, bronchoscopy.

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