# Lung Transplantation

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**Objectives:**

1. To define indications for lung transplantation.
2. To review guidelines for recipient selection for lung transplantation.
3. To describe relative and absolute contraindications to lung transplantation.
4. To describe outcomes following transplantation including survival and physiologic results.
5. To review complications following lung transplantation.
6. To give an overview of the immunosuppressive medications used in lung transplantation.

**Key words:** lung transplantation; acute rejection; obliterative bronchiolitis; cytomegalovirus; immunosuppression

Over the last 15 years, lung transplantation has become a successful therapeutic option for patients with end-stage pulmonary parenchymal and vascular diseases. Dr. James Hardy at the University of Mississippi performed the first lung transplant in 1963. However, the patient only survived 18 days. Subsequent attempts at lung transplantation were complicated by bronchial anastomotic dehiscence and early graft failure resulting in limited survival. Advances in donor and recipient selection, improved surgical techniques, new immunosuppressive drugs, and better management of infections have all contributed to improved survival. Despite these advancements, numerous complications still exist following lung transplantation.

According to the 2001 report from the International Society of Heart Lung Transplantation (ISHLT), over 12,000 lung transplant procedures have been performed worldwide, and in 2000 alone over 1,400 procedures were performed. One-, three-, and five-year survival rates are 72%, 56%, and 43%, respectively, as reported by the Registry of the International Society for Heart and Lung Transplantation.[1] The major rate-limiting factor to long-term survival of lung transplant patients remains infection and chronic rejection.

The majority of lung transplant referrals come from pulmonary physicians outside tertiary transplant centers. With the increase in the number of transplant recipients, much of the subsequent follow-up care is now conducted by the referring pulmonologist for logistical convenience and often as dictated by insurance company mandates. This section will attempt to concisely review the topic of lung transplantation for the pulmonary physician.

## Indications for Lung Transplantation

### *Heart-Lung Transplantation*

One of the original successful lung transplant procedures performed primarily in the late 1980s and early 1990s is heart-lung transplantation (HLT). Currently, HLT is only performed at a few transplant centers and should be reserved for patients who cannot be treated by lung transplantation alone. The most frequent indications for HLT are Eisenmenger's syndrome with a surgically uncorrectable cardiac anomaly or severe end-stage lung disease with concurrent severe heart disease.

### *Bilateral Lung Transplantation*

Bilateral lung transplantation (BLT) is performed for patients with suppurative pulmonary lung disease, *ie* cystic fibrosis and bronchiectasis. In fact, 33% of all BLTs are performed for cystic fibrosis. Initially, double lung transplant was the procedure of choice with the anastomosis performed at the level of the trachea; however, the rate of ischemic airway complications was prohibitive. Now, BLT (essentially sequential SLT) where the anastomoses are performed at the level of the mainstem bronchi, is the preferred surgical technique. Some centers also recommend BLT for younger patients with severe COPD (secondary to tobacco use [20% of BLTs] or $\alpha_1$-antitrypsin deficiency [10% of BLTs]) due to a longer post-transplant life expectancy from increased reserve provided during times of graft complications. In addition, many centers prefer a BLT procedure in patients with primary pulmonary hypertension (9% of BLTs). Although a single lung allograft with normal pulmonary vasculature can accommodate the entire right ventricular output without elevation of pulmonary artery pressures,

in times of graft compromise such as rejection or infection, severe ventilation perfusion abnormalities can develop.

*Single Lung Transplant*

Single lung transplantation (SLT) is performed for obstructive nonsuppurative lung disease such as emphysema secondary to tobacco use or $\alpha_1$-antitrypsin deficiency; 47% and 11% of all SLTs are performed for these indications, respectively. SLT was initially thought to be a poor choice of procedure for COPD patients due to concerns of preferential ventilation to the compliant native lung, but these concerns have proven largely unfounded. Other indications for SLT include idiopathic pulmonary fibrosis (21% of all SLTs), familial pulmonary fibrosis, drug or toxin-induced lung disease, occupational lung disease, sarcoidosis, limited scleroderma, lymphangioleimyomatosisis, eosinophilic granuloma, and other disorders resulting in end-stage fibrotic lung disease. SLT is also performed at some centers for pulmonary vascular disease (4% of SLTs), although the immediate postoperative period can be difficult due to the large volume of blood flow going to the transplanted lung.

The theoretical advantages of SLT include reduced surgical morbidity, shortened hospitalization, and often, the avoidance of cardiopulmonary bypass. This procedure also results in optimization of the use of donor organs, which are in critical shortage.

## Guidelines for Recipient Selection

Any patient with end-stage pulmonary or cardiopulmonary disease with the capacity for rehabilitation can be considered for transplantation (Table 1). The patient should have untreatable end-stage pulmonary disease, no other significant medical illness, and a limited life expectancy. The candidate should be ambulatory with rehabilitation potential. The patient must be psychologically stable, committed to the idea of transplantation, and willing to comply with the rigorous medical protocols and regimens required for successful lung transplant outcome.

**Table 1**—*Guidelines for Recipient Selection for Lung Transplantation**

| | |
|---|---|
| General selection criteria | Untreatable end-stage obstructive or restrictive pulmonary parenchymal or pulmonary vascular disease. |
| | No other significant medical diseases |
| | Substantial limitation of daily activity |
| | Limited life expectancy |
| | Ambulatory with rehabilitation potential |
| | Satisfactory psychosocial profile and emotional support system |
| | Age, yr |
| | HLT $\leq$ 55 |
| | SLT $\leq$ 65 |
| | BLT $\leq$ 60 |
| Relative contraindications | Systemic disease |
| | Colonization with fungus or atypical mycobacteria |
| | High corticosteroid requirements |
| | Significant pleural disease from prior thoracic procedures |
| | Symptomatic osteoporosis |
| | Severe musculoskeletal disease |
| | Mechanical ventilation |
| | Ideal body weight <70% or >130% |
| | Substance addiction in prior 6 mo(including tobacco use) |
| | Psychosocial problems |
| Absolute contraindications | Extrapulmonic disease, *ie*, renal (creatine clearance <50 mL/min) |
| | HIV infection |
| | Malignancy within prior 2 yr |
| | Hepatitis B antigen positivity |
| | Hepatitis C biopsy specimen proven liver disease |

*Modified from: Official American Thoracic Society Statement—June 1992. Lung transplantation: Report of the ATS Workshop on Lung Transplantation. Am Rev Respir Dis 1993; 147:772-776. and adapted from Guidelines for the Selection of Lung Transplant Candidates. Joint Statement of the American Society for International Transplant Physicians / American Thoracic Society / European Respiratory Society / International Society for Heart and Lung Transplantation. Am J Respir Crit Care Med 1998; 158:335-339.

*Age*

Recent international guidelines for selection of transplant candidates[2] suggested age limits of 55 years for HLT, 65 years for SLT, and 60 years for BLT procedures. Although this is somewhat arbitrary, numerous patients with end-stage pulmonary disease are young to middle-age and there is a relative lack of available donors. In addition, older patients have a somewhat poorer outcome than younger patients.

*Relative Contraindications*

*Systemic or Multi-system Disease:* Transplantation is not contraindicated in patients with systemic diseases limited to the lungs such as scleroderma, systemic lupus erythematosus, polymyositis, and rheumatoid arthritis. These cases should be entertained on an individual basis.

Patients with diabetes mellitus, hypertension, or peptic ulcer disease should be evaluated carefully before being considered candidates for lung transplantation, and should only be accepted if their disease is well controlled and there is no resulting end-organ damage.

Patients with active sites of infection are not considered good transplant candidates. Treated tuberculosis and fungal disease pose a particular problem, but are not contraindications for lung transplantation. Many centers will not consider transplanting a patient who is chronically colonized with a resistant organism (*Burkholderia cepacia*, methicillin-resistant Staphylococcus, atypical mycobacterium, or Aspergillus). Centers should try to eradicate these organisms in the pretransplant period and consider each patient on an individual basis. However, if considered, these patients should only be considered for BLT procedures since the colonized remaining lung could pose a serious threat to the new graft in the case of a SLT.

*Corticosteroids:* Initial data implicated corticosteroids as a cause of tracheal bronchial dehiscence. At most centers, patients were required to have completely discontinued corticosteroids. This certainly eliminated a large number of patients with chronic obstructive lung disease and pulmonary fibrosis. More recently, low-dose pretransplant corticosteroids have been proven to be acceptable for patients who cannot have corticosteroids completely discontinued. Currently, most transplant programs will consider patients who can be chronically maintained on ≤20 mg/d of prednisone and may consider patients on higher doses.

*Prior Thoracic Surgery:* Prior thoracotomy or pleurodesis was once considered a relative contraindication to transplantation due to increased technical difficulties and increased bleeding. Despite this, transplantation can be successfully performed in these patients.

*Psychological Criteria:* The patient must be well motivated and emotionally stable to withstand the extreme stress of the pretransplant and perioperative period. A history of noncompliance or significant psychiatric illness is a relative contraindication, although many patients will present with reactive depression or anxiety in the terminal phase of their pulmonary illness.

*Skeletal Disease:* Osteoporosis has become a significant problem in the post-transplant period, and pre-existing symptomatic osteoporosis has been identified as a relative contraindication to transplantation. Bone densitometry should be part of the pretransplant evaluation and treatment initiated in those with evidence of osteoporosis symptomatic or asymptomatic. Nonosteoporotic skeletal disease, such as kyphoscoliosis, is also a relative contraindication to transplantation, primarily because of technical difficulties encountered during surgery.

*Mechanical Ventilation:* Requirement for invasive mechanical ventilation is a strong relative contraindication to transplantation, although lung transplantation has been performed successfully in small numbers of mechanically ventilated patients with cystic fibrosis. However, patients who are on noninvasive ventilatory support can be considered for transplantation.

*Nutritional Status:* In order to be considered for transplantation, patients should have an ideal body weight >70% or <130% of predicted. Those patients with poor nutritional status may be too weak to withstand the surgical procedure; those patients who are obese make more difficult surgical candidates, and may have higher mortality than nonobese patients.[3]

*Substance Abuse:* Drug abuse or alcoholism are considered contraindications to transplantation because these patients are at high risk for noncompliance. Patients who continue to smoke despite end-stage pulmonary disease are not candidates for lung transplantation. Most transplant centers require patients to abstain from cigarette smoking, alcohol abuse, or narcotics for 6 months to 2 years before being considered for lung transplant evaluation.

*Absolute Contraindications*

Recent international guidelines identified several absolute contraindications to lung transplantation including major organ dysfunction, ie, renal (creatinine clearance <50 mL/min), HIV infection, hepatitis B antigen positivity, and hepatitis C with biopsy documented liver disease. Active malignancy within the prior 2 years is also a contraindication to transplantation. For patients with a history of breast cancer greater than stage 2, colon cancer greater than Duke's A, renal carcinoma, or melanoma greater than or equal to level 2, the waiting period should be at least 5 years. Re-staging is suggested prior to transplant listing.

## Disease-Specific Guidelines for Lung Transplantation

One of the most difficult decisions when referring a patient for transplantation is defining the appropriate time or the "transplant window" (Table 2). The potential candidate should be sick enough to have a limited life expectancy, but not so disabled that the individual will be unable to withstand the procedure. Recently, multiorganizational guidelines were established to define the "transplant window" for specific diseases.[2]

*Chronic Obstructive Lung Disease*

The variability in the natural course of COPD makes it especially difficult to predict when patients should be referred for lung transplantation. Based on available data from several large studies determining predictors of mortality in chronic obstructive pulmonary disease, guidelines have been established. The guidelines suggest that patients with COPD are in the transplant window if the $FEV_1$ is <25% of predicted without reversibility with bronchodilator administration, and/or $PaCO_2$ is ≥55 mm Hg and/or cor pulmonale is present. Those patients who are hypercapnic and hypoxemic requiring oxygen supplementation should be given preference. A recent analysis of transplant survival data has shown that patients with COPD may achieve significant improvement in quality of life, but a clear survival benefit with transplantation has not been documented.[4] Rehabilitation and long-term supplemental oxygen, if criteria are met, should be initiated while awaiting lung transplantation.

*Idiopathic Pulmonary Fibrosis*

Based on studies showing the poor survival in patients with idiopathic pulmonary fibrosis and the fact that the majority of patients have a progres-

**Table 2**—*Disease-Specific Criteria for Lung Transplantation**

| | |
|---|---|
| COPD | $FEV_1$ <25% of predicted (nonreversible)<br>$PaCO_2$ ≥55 mm Hg<br>Cor pulmonale<br>$O_2$-dependent hypercapnic patients (refer early) |
| IPF | Symptomatic disease despite medical therapy<br>Abnormal pulmonary function:<br>VC ≤ 60 to 70% of predicted<br>Diffusing capacity ≤ 50 to 60% of predicted |
| CF | $FEV_1$ ≤ 30% of predicted<br>Clinical deterioration with $FEV_1$ > 30% of predicted<br>$PaCO_2$ > 50 mm Hg<br>$PaO_2$ on room air <55 mm Hg<br>Young, female patients (refer early) |
| PPH | NYHA III-IV despite vasodilator treatment<br>Cardiac index < 2 L/min/$m^2$<br>Right atrial pressure > 15 mm Hg<br>Mean pulmonary artery pressure > 55 mm Hg |
| Eisenmenger's | NYHA III-IV despite medical treatment |

*Adapted from: Guidelines for the selection of lung transplant candidates: joint statement of the American Society for International Transplant Physicians/American Thoracic Society/European Respiratory Society/International Society for Heart and Lung Transplantation.[2]
IPF=idiopathic pulmonary fibrosis; VC=vital capacity; NYHA=New York Heart Association.

sive downhill course despite standard immunosuppressive therapy, patients with pulmonary fibrosis should be referred for transplantation early. In fact, this is the group of patients who have the highest mortality while on the transplant list. The recent international guidelines suggest that these patients should be referred when they have symptomatic disease and have failed standard immunosuppressive therapy and/or abnormal pulmonary function even with minimal symptoms, *ie*, vital capacity ≤60% to 70% of predicted and/or diffusing capacity ≤50% to 60% of predicted and/or rest or exercise desaturation.

*Cystic Fibrosis*

Although there has been an improvement in life expectancy for patients with cystic fibrosis (CF), most patients still succumb to respiratory failure and cor pulmonale. The international guidelines have suggested that the following criteria be used to define the transplant window for CF patients: an $FEV_1 \leq 30\%$, or an $FEV_1 > 30\%$ with progressive deterioration such as increasing hospitalizations, rapid deterioration in $FEV_1$, cachexia and/or massive hemoptysis, a $PaO_2$ <55 mm Hg on room air, and/or a $PaCO_2$ >50 mm Hg. Female patients and patients <18 years old have a more progressive course and should be considered for lung transplantation earlier. Recently, a predictive model for selecting patients with CF has been proposed to more accurately predict the survival effect of LT in these patients.[5] The model includes: age, sex, $FEV_1\%$, weight for age Z score, the presence of pancreatic sufficiency, diabetes mellitus, infection with *S. aureus* or *B. cepacia*, and the number of acute exacerbations requiring treatment.

Cystic fibrosis patients are often colonized with multiple resistant organisms defined as resistant to all agents in two of the following classes: the ß-lactams, aminoglycosides, and/or quinolones. Pan-resistant colonization includes organisms resistant *in vitro* to all groups of antibiotics particularly *P. aeruginosa* and *B. cepacia*. A recent study[6] examined the outcome of CF patients with pan-resistant *P. aeruginosa* and *B. cepacia* versus those with susceptible organisms. Postoperative ventilator days, length of hospital stay, and antibiotic days were similar between groups. The incidence of bronchitis and pneumonia were also comparable between these two groups; 1-yr survival was comparable, 81% and 83%, respectively. However, a subanalysis of those patients with *B. cepacia* had a lower 1-yr survival of 50% in comparison to resistant *P. aeruginosa*, 90%. Another study found a 1-yr survival of 67% for *B. cepacia* positive CF patients as compared to 97% in *B. cepacia* negative CF patients.[7] Some newer data suggest that those patients colonized with *B. cepacia* of the genomovar III type have a particularly poor prognosis.[8] Thus, colonization with *B. cepacia* genomovar III should be considered a strong relative contraindication for transplantation.

*Primary Pulmonary Hypertension*

Based on extrapolation from data from the National Heart Blood and Lung Transplant Registry for primary pulmonary hypertension, selection guidelines have been established for patients with PPH. These guidelines suggest that patients in New York Heart Association Class III or IV, despite optimal therapy including vasodilators such as prostacyclin or calcium channel blockers, and those with significantly elevated pulmonary artery pressures (PA mean >55 mm Hg), depressed cardiac index (<2 $L/min/m^2$), or a right atrial pressure of >15 mm Hg should be considered for transplantation. Other patients should be followed closely and re-assessed for transplantation at 6-month intervals.

*Pulmonary Hypertension Secondary to Congenital Heart Disease (Eisenmenger's Syndrome)*

Patients with this type of secondary pulmonary hypertension have been found to have a significantly better prognosis than those patients with primary disease. Therefore, due to individuality of progression with this disease, precise criteria for transplantation have not been established. In general, patients are usually referred to transplant centers when they are in New York Heart Association Class III or IV.

## Pretransplant Evaluation

Once a patient is deemed a potential candidate for transplantation, several studies are usually performed for further assessment. Typically, these include pulmonary function tests, including lung volumes, spirometry and diffusing capacity, and a measure of exercise performance such as a 6-minute walk. Cardiac evaluation includes an

electrocardiogram, and an echocardiogram, in addition to a functional cardiac study such as dobutamine echocardiography and/or coronary angiography in patients >40 years of age or those with significant risk factors for coronary artery disease. A high-resolution CT is often obtained to look for bronchiectasis, which could indicate the necessity for a bilateral procedure, or to look for focal nodules not apparent on plain chest radiographs. Renal and liver functions are assessed by 24-hr creatinine clearance and liver function tests, respectively. Serologies for hepatitis and HIV should also be obtained. The majority of these investigations can be performed at the referring center. In those patients being evaluated for single lung transplant, a ventilation/perfusion scan with quantitation may suggest the preferential side to be transplanted if there is unequal distribution of perfusion.

While awaiting transplantation, patients should have close follow-up with the transplant center or their referring physician for both physiologic and emotional support. In those patients who are pretransplant for suppurative lung disease, sputum cultures should be obtained at 3-month intervals to assist in the antibiotic regimen in the immediate postoperative period. Those patients who are able should be involved in a rehabilitation program prior to transplantation.

## Donor Allocation

As established by The United Network of Organ Sharing, lungs are allocated primarily by time on the waiting list, and not by necessity. Organs are first distributed locally, then regionally, and finally nationally. Currently, the average time on the waiting list is approximately 18 months and therefore close management of the listed transplant patient is required. Despite this close attention, a significant percentage of patients die while awaiting transplantation.

## Living Donor Transplantation

Several institutions worldwide are now performing living donor transplantation. The primary indication for living donor transplantation is cystic fibrosis. Generally, two blood group compatible living donors each provide a lower lobe to the recipient. Ideally, the donors should be larger than the recipient so that the donor lobes fill the hemithorax. This procedure is not yet performed at the majority of lung transplant centers due to certain technical and ethical issues involved. Early data suggest that outcomes in these patients are comparable to those reported with cadaveric donor lung transplants.

## Donor Criteria

Donor organ shortage remains the greatest limiting factor in the numbers of lung transplantations performed. The majority of potential lung donors are brain dead, and as stated above, only a small number of living related lung transplant procedures have been performed. The usual donor selection criteria include age younger than 60-65 years, no history of significant lung disease, and a limited smoking history. In addition, potential donors should have clear lung fields on chest roentgenograms and adequate gas exchange as assessed by $Pao_2$ >300 mm Hg on an $Fio_2$ equal to 1 and a PEEP of 5 cm $H_2O$ or a $Pao_2$ to $Fio_2$ ratio >250-300 mm Hg. A normal sputum Gram stain and/or endobronchial inspection is also part of the donor evaluation examination. Marginal donors, *ie*, those not meeting all of the above criteria, are being used more frequently to expand the donor pool.[9,10] Donors are excluded from potential lung donation if they have evidence of active infection, HIV, hepatitis, and/or malignancy. Donor and recipient compatibility is assessed by matching by A, B, O blood type and chest wall size. HLA matching is not routinely performed in lung transplantation.

## Surgical Procedure

For a single lung transplant, the recipient surgery is performed via a posterolateral thoracotomy incision. The recipient left atrium and donor pulmonary vein are anastomosed first, followed by the bronchial anastomosis, and finally the arterial anastomosis. Bilateral lung transplantation is usually performed through a transverse thoracosternotomy (clam shell incision). Cardiopulmonary bypass may be required for cases of pulmonary hypertension. Organ preservation remains a major area of research in lung transplantation. Currently, the lung can only be preserved for a period of approximately 4-6 h without suffering significant

ischemia-reperfusion injury. Newer preservative agents may increase this time period and permit a larger area for donor allocation.

## Management After the Postoperative Period

Patients are typically discharged from the hospital within 7-14 days following surgery. Follow-up is in the outpatient clinic on a weekly, biweekly, and finally monthly basis. Following this, patients often return home for follow-up with the referring pulmonologist. Weekly monitoring includes levels of immunosuppressive medications such as cyclosporine or tacrolimus, a complete blood cell count to monitor leukocytes and platelet counts because of azathioprine or mycophenolate mofetil, blood chemistry to follow creatinine because of cyclosporine or tacrolimus, a chest radiograph, routine spirometry and exercise oximetry, or 6-min walk. In addition, patients are given home spirometers and are instructed to bring in their home spirometry measurements at each visit.

Some institutions perform surveillance bronchoscopy on a routine schedule to detect asymptomatic rejection or infection, while other institutions reserve this procedure for clinical deterioration, without compromised survival or rates of BOS.[11] The chest radiograph has not been shown to be specific for early detection of rejection or infection.

Close monitoring of pulmonary function has also been studied as a way of detecting graft complications. PFTs have been shown to have very low specificity and good sensitivity (85%) for detection of graft complications, but again are unable to distinguish rejection from infection. Therefore, pulmonary function tests remain the most sensitive test in the late postoperative period for detecting infection or rejection, although they cannot differentiate between these or other possible complications.

## Outcome

### *Survival*

Actuarial survival following transplantation is reported at 88%, 72%, 56%, and 43% for 1 month, 1, 3, and 5 years, respectively, as reported to the ISHLT Registry in 2001, and are significantly lower than those reported for other types of solid organ transplant recipients.[1] Early mortality, *ie*, <90 days, is most often due to infection and late mortality, *ie*, >90 days, is most often related to rejection. Risk factors associated with death within the first year as determined by multivariate analysis include a diagnosis of pulmonary hypertension, pretransplant ventilator dependence, and recipient age >50 years. Until recently, there was no apparent survival difference between those patients undergoing SLT or BLT. However, it now appears that BLT recipients may have a survival advantage beginning at 3 years post transplant. Patients undergoing HLT do have lower survival rates. Survival rates are higher for patients undergoing lung transplantation for COPD in comparison to those patients undergoing transplantation for idiopathic pulmonary fibrosis or primary pulmonary hypertension, and older patients have a poorer long-term survival. Younger (<50-60 years old) COPD patients undergoing BLT appear to have a survival advantage over those undergoing SLT.

### *Physiologic Results*

The degree of improvement in lung function postoperatively is the product of many factors. In the uncomplicated transplant recipient, one can expect a gradual improvement and ultimate plateau of lung function by 3-6 months following the procedure. In patients receiving a single lung, the $FEV_1$ can be expected to improve to 50% to 70% of predicted. SLT for nonseptic obstructive lung disease results in moderate residual obstructive pulmonary dysfunction on spirometry. SLT in patients with underlying restrictive lung disease can be expected to have mild residual restrictive physiology. These results likely reflect the physiology of the remaining obstructed or restricted lung. Following SLT procedures, the majority of the ventilation and perfusion go to the transplanted lung. BLT procedures usually result in normal spirometry with an equal division of ventilation and perfusion. Those patients who undergo transplantation for PPH have no significant change in pulmonary function, marked improvement in gas exchange, and near-normal hemodynamics following transplantation, including near-complete recovery of right ventricular function.

The majority of those patients who undergo either lung transplant procedure without complications are able to carry out activities of daily

living without compromise, although formal cardiopulmonary exercise testing generally reveals a reduction in maximum oxygen consumption to 40% to 60% of predicted in all transplant groups. The reasons for this remain unclear and do not appear to be cardiac or pulmonary in origin. The leading physiologic hypothesis is that the immunosuppressive agents may have an effect on peripheral skeletal muscles, resulting in impaired peripheral oxygen utilization.

*Quality of Life*

Quality of life (QOL) issues are a relatively recent area of research in lung transplantation. Several small studies have shown improvement in overall health-related QOL. The large majority of patients have expressed satisfaction with their transplant decision. Even if survival benefit is in question, the improvement in QOL may be worth the sacrifice to many patients. Of interest, fewer than 40% of patients return to work on a part-time or full-time basis following transplantation.

## Complications

Figure 1 shows some of the common post-transplant complications, and the approximate time period in which they usually occur.

*Pulmonary Reimplantation Response*

The most significant early postoperative complication following lung transplantation is the development of the pulmonary reimplantation response (PRR) or primary graft failure. It is estimated that up to 80% of patients will experience some degree of reimplantation injury, and in 15% of patients this can be severe. The PRR can persist for hours to days following the surgery. The PRR

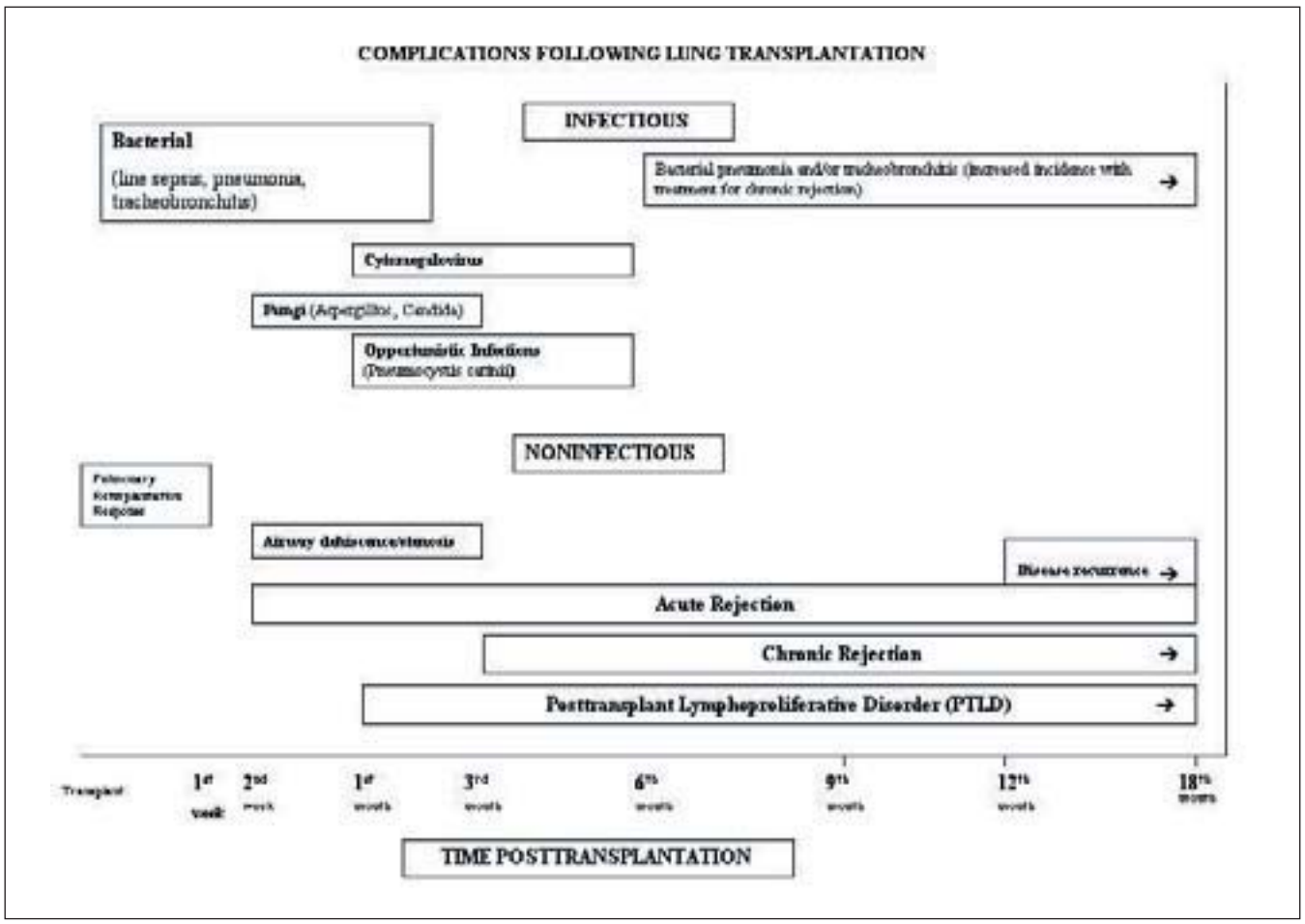


**Figure 1.** The common complications following lung transplantation and the typical time periods in which they develop. Reprinted from Melo J, Levine SM: Lung transplantation for the referring pulmonologist. PCCU 1999; volume 13, lesson 16. Used with permission.

is characterized clinically by new radiographic infiltrates, a decrease in pulmonary compliance, and disrupted gas exchange. Radiographic findings include patchy alveolar consolidation and/or dense perihilar haze and lower lobe alveolar consolidation. The typical course of the PRR includes progressive worsening; or stabilization over the subsequent 2 to 4 days followed by resolution. It is thought that the likely mechanism for the PRR is ischemia reperfusion injury. Management includes differentiation of other perioperative complications such as volume overload, rejection, infection, and venous anastomotic problems. The latter can be evaluated with a transesophageal echocardiogram. Treatment includes supportive care and diuretics. Reports have documented successful use of nitric oxide and/or extracorporeal membrane oxygenation in these patients.

One study examined patients with primary graft failure.[12] They found an incidence of 15% of this complication and it was associated with a prolonged hospital course, prolonged mechanical ventilation, a poor 1-yr survival (40% vs 69%) and compromised function among survivors. The authors found no clear risk factors for primary graft failure including age, sex, underlying disease, pulmonary artery pressure, type of transplant procedure, ischemic times, or use of cardiopulmonary bypass. The study did note that induction immunotherapy was used less frequently in those patients who developed primary graft failure. A study from a different large transplant center identified cardiopulmonary bypass as a risk factor for PRR and also observed prolonged mechanical ventilation and ICU stays in those patients with PRR, but did not observe a difference in survival rates between patients with and without PRR.[13]

Hemorrhage and phrenic nerve paralysis have also been reported in the early postoperative period.

*Airway Complications*

Airway problems were significant causes of morbidity and mortality following early attempts at lung transplantation, and developed in 20% to 50% of transplant recipients. Airway complications can be divided into the early and late time periods. Early airway complications usually develop during the first 4-8 wks and present as a partial or complete anastomotic dehiscence and/or fungal (usually Aspergillus or Candida) or bacterial (usually Staphylococcus or Pseudomonas) anastomotic infection and can subsequently result in anastomotic strictures. Bronchomalacia can also develop.

Theoretical causes of airway complications include ischemia at the site of the anastomosis, infection, poor organ preservation, and/or rejection. Since revascularization of the bronchial circulation is generally not performed following lung transplantation, anastomotic techniques such as the omental or pericardial fat wrap, where an intact portion of omentum or pericardial fat is wrapped around the bronchial anastomosis, or the telescoping anastomotic technique, where one bronchus is overlapped 1-2 cartilaginous rings within the larger bronchus to improve blood flow, have been developed. These have resulted in a decrease in the incidence of anastomotic complications to 10% to 20%, with low mortality and morbidity.

Clinically, bronchial anastomotic complications, including stenosis and bronchomalacia, can present with cough, shortness of breath, wheezing, dyspnea on exertion, and worsening obstruction on pulmonary function testing. The characteristic flow volume loop demonstrates a concave appearance in both the inspiratory and expiratory loops. Bronchial strictures or stenoses may also be visualized on chest radiographs, CT, and/or bronchoscopy. Partial or complete bronchial dehiscence can also present with mediastinal emphysema on chest radiograph or air adjacent to the bronchial anastomosis on CT.

Therapeutic options for anastomotic complications include balloon dilation of a stricture, stent placement, laser, and rarely, surgery. If anastomotic infection with fungal or bacterial organisms is suspected bronchoscopically or diagnosed by endobronchial washing, brushing or biopsy culture, or histology, then appropriate antibiotics should be instituted.

*Rejection*

Graft rejection is categorized clinically according to the time of onset following transplantation and the histopathologic pattern. The three types of rejection are hyperacute, acute, or chronic. Hyperacute rejection is mediated by pre-existing alloantibodies that immediately bind to donor vascular epithelium, leading to vessel thrombosis via complement activation. Fortunately, this is a rare complication in lung transplantation and will not be discussed further.

*Acute Rejection:* Acute rejection can develop in up to 50% of patients in the first postoperative month, and as many as 90% of patients will have at least one episode of acute rejection within the first year. The typical time period for acute rejection is between 10-90 days following lung transplantation. It is not uncommon (20%) for a single patient to experience 2-3 episodes within the first few months following transplantation either recurrent (>2 episodes) or persistent (failure to resolve with standard therapy). Acute rejection is usually not seen as frequently after the first year following transplantation. Risk factors for acute rejection are poorly defined, but HLA mismatches may have a correlation.

Clinically, acute rejection presents with cough, shortness of breath, malaise, and fever. Occasionally, the presentation is asymptomatic and some centers advocate surveillance bronchoscopy to detect this, although outcome data are not available. Physical examination may reveal rales or wheezing. The utility of the chest radiograph depends upon the time after transplantation. Typically, in the first month the chest radiograph can be abnormal in up to 75% of rejection episodes; however, in those episodes of rejection occurring after 1 month post-transplantation, only 25% of cases have an abnormal radiograph. The most common radiographic patterns noted with acute rejection include a perihilar flare, alveolar, or interstitial, localized or diffuse infiltrates with or without associated pleural effusion.

Physiologic findings during periods of acute rejection include hypoxemia and deterioration in pulmonary function. Pulmonary function abnormalities are characterized by a decline in $FEV_1$ of at least 10% to 15% from baseline as well as a decline in the forced expiratory flow over 25% to 75% of expired vital capacity of >10%-15%. Once again, these changes are nonspecific and can also be seen with infectious etiologies.

Since clinical criteria alone cannot differentiate between acute rejection, infection, and less common graft complications, transbronchial biopsy with bronchoalveolar lavage has emerged as the primary procedure for diagnosis. Diagnosis of acute rejection by transbronchial biopsy has ranged from 61% to 94%, and specificity from 90% to 100%. A histologic grading system for acute pulmonary rejection was initially proposed in 1990 and revised in 1996.[14] Pathologically, acute rejection is characterized by perivascular, mononuclear lymphocytic infiltrates with or without airway inflammation, and is graded histologically A0-A4 based on the degree of perivascular inflammation. In addition, airway involvement with lymphocytic bronchitis or bronchiolitis can develop and is graded B0-B4. As rejection progresses, the perivascular lymphocytic infiltrates surrounding the venules and arterioles become dense and extend into the perivascular and peribronchiolar alveolar septa. In severe rejection, the alveolar space may be involved and parenchymal necrosis, hyaline membranes, and necrotizing vasculitis have been described.

Once acute rejection has been diagnosed, treatment consists of augmentation of immunosuppression. Methylprednisolone (10-15 mg/kg/day IV for 3 days) followed by an increase in the maintenance prednisone regimen to .5-1 mg/kg/day with a taper over the next several weeks is a standard treatment regimen. Maintenance immunosuppression should also be augmented. Typically, resolution of symptoms occurs in days, and histologic follow-up in 3-4 weeks should show resolution. Recurrent or persistent acute rejection may initiate conversion in the baseline immunosuppression regimen. Lympholytic therapy, methotrexate, photophoresis, total lymphoid irradiation, and/or aerosolized cyclosporine have been used with variable success. Mycophenolate mofetil initiated *de novo* has resulted in a decreased incidence of acute rejection in several small studies.

*Obliterative Bronchiolitis:* Chronic rejection has been equated with the histologic finding of obliterative bronchiolitis (OB), and remains a major cause of morbidity and mortality after lung transplantation and the leading single cause of death after the first post-transplant year. The current incidence of OB ranges from 35% to 50% among different centers. OB has been defined clinically by an obstructive functional defect and histologically by obliteration of terminal bronchioles. The mean time to diagnose OB is 16-20 months following the lung transplant procedure, but has been reported as early as 3 months after transplantation. More than 50% of recipients will develop some degree of OB by 5 years post-transplant.

The etiology and risk factors for OB remain unclear. Several possible causes have been proposed including uncontrolled acute rejection, lymphocytic bronchiolitis, CMV pneumonitis, CMV infection without pneumonitis, HLA-A mismatches, total

HLA mismatches, absence of donor antigen-specific hyporeactivity, non-CMV infection, older donor age, and bronchiolitis obliterans with organizing pneumonia. The most consistently identified risk factor is acute rejection, particularly in those patients who experience recurrent, high-grade episodes of acute rejection. It is probable that lymphocytic bronchiolitis and cytomegalovirus pneumonitis are also important risk factors for OB.[15,16]

Clinically, OB can manifest as an upper respiratory tract infection and can be mistakenly treated as such. Other patients present without clinical symptoms but with gradual obstructive dysfunction on pulmonary function testing. $FEV_1$ has been the standard spirometric parameter used, but midexpiratory flow rates may be a more sensitive parameter for early detection.

Typically, chest radiographs are not helpful in the diagnosis of OB because most patients have radiographs unchanged from their baseline post-transplant radiographs. High-resolution CT may reveal peripheral bronchiectasis, patchy consolidation, decreased peripheral vascular markings, air trapping, and bronchial dilation, which may aid in the diagnosis of OB. Air trapping on end-expiratory high-resolution CT has been shown to be a sensitive (91%) and accurate (86%) radiologic indicator of OB, but may not be able to provide an early diagnosis of this disorder.[17] Bronchoalveolar lavage neutrophilia, exhaled nitric oxide levels, bronchial hyperresponsiveness, and increased nitrogen washout may also be surrogate markers of BOS.

As with acute rejection, transbronchial biopsy is used to diagnose OB, but primarily to exclude other diagnoses. The classic pathologic finding is constrictive bronchiolitis. Unfortunately, the sensitivity for the diagnosis of OB by transbronchial biopsy is low (range 15%-87%) and the diagnosis of OB is often made by exclusion and graded physiologically based on the degree of change in pulmonary function ($FEV_1$) from baseline. Because of the variability in obtaining bronchioles by transbronchial biopsy, the International Society of Heart Lung Transplantation has established a bronchiolitis obliterans syndrome (BOS) staging system.[18] This staging is based on a reduction in $FEV_1$ in comparison to a post-transplant baseline $FEV_1$ with or without the pathologic documentation of OB (Table 3). This staging system is currently under revision by the International Society of Heart and Lung Transplantation, and the proposed new system will include an earlier BOS category of potential BOS using changes in $FEV_1$ and/or mid flows as compared to post-transplant baseline values ($FEV_1$ 81%-90% of baseline and/or $FEF_{25-75}$ ≤75% of baseline).[16]

Once OB has been diagnosed histologically or clinically by exclusion of alternate diagnoses, treatment is begun with high-dose methylprednisolone followed by a tapering course of oral corticosteroids. Lympholytic agents such as antilymphocyte globulin (ALG), monoclonal antibody to the $CD_3$ lymphocyte receptor ($OKT_3$), or anti-IL2 agents such as daclizumab can be considered if there is no clinical response to steroid treatment. Therapy may stabilize pulmonary function, but uncommonly results in significant improvement. Other common physiologic scenarios may be relentless deterioration in pulmonary function despite therapy, gradual steady deterioration in pulmonary function, or a series of drops with plateaus. Alternate immunosuppressive agents such as mycophenolate mofetil, tacrolimus, and sirolimus have also been associated with stabilization of pulmonary function when used as rescue treatment for BOS. Methotrexate, total lympholytic radiation, aerosolized cyclosporine, photophoresis, and newer immunosuppressive agents have been used in refractory cases of OB. Inhaled corticosteroids may be added in cases of lymphocytic bronchiolitis.

Infection, including bronchiectasis, frequently complicates intensive immunosuppression for OB and may result in death. Pseudomonas is a common offender and aerosolized aminoglycoside antibiotics or suppressive quinolone treatment may be considered. Bronchomalacia can also develop. Survival after diagnosis of OB was reported at 74%, 50%, and 43% at 1, 3, and 5 years, respectively, in one small series.[19] Since most cases of OB can only

**Table 3**—*Clinical Staging System for Obliterative Bronchiolitis**

| Stage† | $FEV_1$ |
|---|---|
| 0 – No significant OB | ≥ 80% of baseline |
| 1 – Mild OB | 66 to 80% of baseline |
| 2 – Moderate OB | 51 to 65% of baseline |
| 3 – Severe OB | ≤ 50% of baseline |

* Adapted from Cooper JD, Billingham M, Egan T, et al: A working formulation for the standardization of nomenclature and for clinical staging of chronic dysfunction in lung allografts. J Heart Lung Transplant 1993; 12:713-716.

† Each stage is subdivided into a and b, where a is without histologic documentation of OB and b is with histologic documentation of OB. Adapted from International Society for Heart and Lung Transplantation staging system

be stabilized, strategies directed at prevention, early diagnosis, and treatment are necessary for preservation of lung function. Retransplantation has been performed with variable results. Survival is somewhat less than that for *de novo* transplants. In addition, the limited donor supply does not allow for the common practice of this procedure.

*Infectious Complications*

Infections have been a major cause of early and late morbidity and mortality following transplantation and remain the leading single specific cause of death in the first post-transplant year. The incidence of infection is significantly higher than that reported in other solid organ recipients and may be related to continuous environmental exposure of the allograft. Other predisposing factors include diminished cough reflex secondary to denervation, poor lymphatic drainage, decreased mucociliary clearance, recipient harbored infection, and occasionally, transfer of infection from the donor organ. Nosocomial infections at the site of the surgical wound, vascular access, urinary tract or ventilator-associated pneumonias also occur in the early postoperative period. In most circumstances, the allograft is the primary location of infection.

*Bacterial Infections:* Bacterial pneumonia is the most common life-threatening infection to develop in the early postoperative period and had been reported to have an incidence as high as 35% in the first two postoperative weeks. Common organisms include *P. aeruginosa* and *S. species.* The incidence of perioperative bacterial pneumonia has been decreased to as low as 10% by broad-spectrum antibiotic prophylaxis, usually an antipseudomonal cephalosporin and clindamycin, and routine culture of the trachea of the donor and the recipient at the time of the surgery. Prophylactic antibiotics are usually discontinued at 3 days if cultures are negative and tailored to the cultured organisms if positive. Patients transplanted with bronchiectasis usually have postoperative bacterial prophylaxis continued for 7 days. The prevalence of bacterial pneumonia remains high during the first 6 months following transplantation and decreases subsequently, although a second late peak in incidence often occurs during augmentation of immunosuppression for treatment of chronic rejection. Bacterial infection due to Staphylococcus or less commonly, Pseudomonas, can develop at or distal to the site of the anastomosis in the early post-transplant period. Of interest, the incidence of lower respiratory infections does not appear to be increased in patients transplanted for cystic fibrosis in comparison to patients transplanted for other indications.

It is often difficult to distinguish pneumonia from other early graft complications such as reperfusion injury, pulmonary edema, rejection, and other infectious etiologies. In addition, differentiation between colonization and invasion may be difficult and often requires invasive procedures such as bronchoscopy with bronchoalveolar lavage, quantitative sterile brush sample, and/or transbronchial biopsy.

*Other Early Infections:* Atypical pneumonias such as Legionella, Mycobacteria, and Nocardia are uncommon in lung transplantation, but have been reported to occur in 2% to 9% of recipients. Viral infections, such as those due to herpes simplex virus, have been significantly reduced with the common use of acyclovir or ganciclovir prophylaxis. Candidal infections may be seen in the early postoperative period, but usually do not cause invasive disease.

Trimethoprim sulfamethoxazole prophylaxis (usually on a 3x/wk schedule) has significantly reduced the incidence of *Pneumocystis carinii* pneumonia to <1% in the lung transplant recipient.

*Viral Infections – Cytomegalovirus:* In the period 1 to 6 months following transplantation, cytomegalovirus (CMV) accounts for the majority of the viral infections in lung transplant recipients. The typical time period for development of CMV infection is 30-150 days postoperatively with an incidence of illness (*ie*, infection and disease) of approximately 50%. Risk factors for CMV disease are dependent on the serology of the donor and recipient as well as the use of high-intensity immunosuppressive therapy, including cytolytic therapy. CMV-positive recipients from either positive or negative donors develop CMV disease approximately 25%-35% of the time, while CMV-negative recipients have a 85% chance of developing disease when implanted with a CMV positive lung. There are some data showing that CMV pneumonitis may contribute to the development of chronic rejection.

CMV can cause a wide spectrum of disease from asymptomatic infection, *ie*, shedding of the virus in the urine or BAL to widespread dissemination. Various presentations of CMV in lung transplant

patients can include pneumonitis – most commonly, gastroenteritis, hepatitis, and colitis. CMV pneumonitis can often be confused with acute rejection. Clinical findings of CMV pneumonitis include fever, cough, hypoxemia, an interstitial or alveolar infiltrate, and leukopenia. Diagnosis of invasive disease requires cytologic or histologic changes in cell preparation or tissue. Therefore, fiberoptic bronchoscopy with transbronchial biopsy and BAL is often necessary and can diagnose 60% to 90% of patients with CMV pneumonia. The diagnosis of CMV infection may occasionally be made on the basis of positive cultures and the compatible clinical setting after other causes of pulmonary disease have been excluded bronchoscopically. The pathologic hallmark of CMV infection is a cytomegalic 250-nanometer cell containing a large central basophilic intranuclear inclusion. This inclusion is referred to as an "owl's eye" because it is separated from the nuclear membrane by a halo. These inclusions may be well seen on hematoxylin-eosin or a Papanicolaou's stain. Identification of CMV cytologically is very specific (98%), but lacks sensitivity (21%) for the presence of infection. Other pathologic findings in the lung parenchyma include a lymphocytic and mononuclear cell interstitial pneumonitis.

Ganciclovir is currently the main stay of therapy for invasive CMV disease. Initial doses of 5 mg/kg twice daily for 3-4 wks have been shown to reduce mortality from 60% to 80% to 15% to 20% in symptomatic CMV pneumonitis. Bone marrow toxicity is one of the major limiting side-effects of ganciclovir and may require conversion to an alternate agent such as foscarnet. Some centers also use CMV-specific hyperimmune-globulin in the treatment of CMV disease.

Prophylaxis against CMV infections has become a major strategy in most transplant centers. Initially, some centers attempted to match CMV-negative recipients with CMV-negative donors when possible; however, the limited donor supply did not allow the continuation of this practice. The use of CMV-negative blood products is advocated. Ganciclovir prophylaxis does seem to be effective in delaying the onset of CMV infection. At some centers, prophylaxis is given only to the CMV mismatched patients, *ie*, a negative recipient receiving an organ from a positive donor. Other centers prophylax all but the negative-negative patient group. Prophylactic treatment approaches usually include 2-4 wks of ganciclovir (5 mg/kg q.d.), although some centers continue prophylaxis up to 90 days, particularly in the donor-positive recipient negative subset of patients. In the highest risk groups, CMV hyperimmunoglobulin may be added. The recently available oral form of ganciclovir may be of potential use in the lung transplant population, but data are inconclusive. Pre-emptive strategies such as initiation of treatment when a high level of CMV blood antigenemia is detected may also delay and decrease the severity of CMV infection, and may become the standard of care.

Other viral infections that have been described in the lung transplant patient include herpes simplex virus (early post-transplant) respiratory syncytial virus, other paramyxoviruses (such as parainfluenza), influenza, and adenovirus. Acyclovir prophylaxis for herpes infection is initiated at most programs after discontinuation of ganciclovir.

*Fungal Infections:* Fungal infections are more common in the lung transplant recipient than in those with other solid organ transplants. The overall incidence of invasive fungal infection in lung transplantation ranges from 10% to 22% and usually develops in the first few months after transplantation. Fungal infections account for the most significant morbidity and mortality of all infectious agents following transplantation and mortality can range from 40% to 70%.

Aspergillus species including *A. fumigatus*, *A. flavus*, *A. terreus*, and *A. niger* can be colonizing organisms or can result in infection presenting as indolent, progressive pneumonia or as an acute fulminant infection that rapidly disseminates. Aspergillus exhibits the propensity to invade blood vessels and may present as an infarct or with hemoptysis. The radiographic findings of pulmonary aspergillosis include focal, lower lobe infiltrates, patchy bronchopneumonic infiltrates, single or multiple nodules with or without cavitation, thin wall cavities, and opacification of the entire lung graft. High-resolution CT scan may reveal a halo sign thought to be pathognomonic for invasive aspergillosis. Other forms of presentation of aspergillus infection can include pseudomembranous tracheobronchitis often at, and distal to, the site of the anastomosis. Diagnosis of invasive aspergillosis requires identification of organisms within tissues. These organisms can appear as septated hyphae that branch at acute angles and can be detected on hematoxylin-eosin and methenamine silver stains.

Survival with Aspergillus infection has been improved with the early initiation of high-dose amphotericin and a reduction in immunosuppressive therapy. Surgical resection may occasionally be required to maximize cure rates in patients with aspergillosis. A lipid formulation of amphotericin B should also be considered in the management of invasive fungal infections in patients who are intolerant or develop nephrotoxicity with conventional amphotericin B, and in patients with progressive fungal infection despite therapy with conventional amphotericin. Prophylaxis with amphotericin B, azoles (particularly itraconazole for 3-6 months), or aerosolized amphotericin has shown promise in decreasing the incidence of Aspergillus infection post-transplant.

Candida species can cause a variety of syndromes in the lung transplant patient including mucocutaneous disease, line sepsis, wound infection, and rarely pulmonary involvement. Fluconazole has emerged as an effective alternative for infections caused by *Candida albicans*, but amphotericin B is still the agent of choice for a widespread disease. Fluconazole appears to be less active against other Candida species such as *C. glabrata* and C. *krusei*.

Other rare causes of fungal infection in lung transplant recipients have included *Cryptococcus neoformans* as well as the dimorphic fungi such as coccidioides, histoplasma, and blastomyces. Amphotericin B remains the antifungal agent of choice for these infections, although azole agents can be used for maintenance.

*Mycobacteria:* Mycobacterial disease both typical and atypical have been successfully treated in the lung transplant patient.

*Vaccinations:* Standard vaccination regimens should be used in the lung transplant population.

### *Post-Transplant Lymphoproliferative Disorders*

Post-transplant lymphoproliferative disorders (PTLD) are reported more frequently following lung transplantation than in other solid-organ transplant recipients. Lymphomas comprise a majority (22%) of PTLDs. The PTLDs are comprised of a heterogeneous group of lymphoid proliferations of variable clonality. The B cell non-Hodgkin's lymphoma are the most frequent form of PTLD and have been associated with Epstein-Barr virus activity either serologically or by identification of viral DNA in tissue. There is no clear correlation between episodes of rejection, specific immunosuppressive drugs and the development of PTLD. The incidence of PTLD following lung transplantation has been reported to range between 4.6% and 9.4%. Those patients who have negative EBV serology prior to transplantation and receive an organ from an EBV-positive donor resulting in seroconversion are at a significantly higher risk for developing PTLD. Children are at higher risk due to their frequent EBV-negative status.

Clinical features of PTLD in lung transplant recipients include development in the first post-transplant year, involvement of the allograft, and radiographic findings of solitary or multiple pulmonary nodules. Disseminated disease has also been reported. Treatment includes a reduction in immunosuppression as well as adjunctive treatment with antiviral therapy, radiation, chemotherapy, surgery, and adoptive immunotherapies extrapolated from the bone marrow transplant population. Mortality may be significant with high-grade PTLD. An increased incidence of other nonlymphomatous malignancies is reported in the lung transplant population, and careful screening is recommended.

### *Miscellaneous Complications*

Recurrence of primary disease has been described in patients transplanted for sarcoidosis, lymphangiomymatosis, giant cell interstitial pneumonitis, and diffuse panbronchiolitis. However, disease recurrence may be an incidental finding in these patients.

Pleural effusions may develop either due to the fact that the lymphatics are not re-anastomosed post-transplant and/or in the setting of rejection. Prolonged postoperative air leaks are well described.

Gastroparesis and an increased incidence of gastrointestinal emergencies are also described in lung transplant recipients.

Osteoporosis remains a significant problem in the post-transplant period and is best managed with bisphosphonates such as alendronate or pamidronate.[21,22]

Deep venous thrombosis and pulmonary embolism were reported to have an incidence of 12% in one series of lung transplant recipients.

## Immunosuppression

Since transplantation of a lung graft into a recipient invokes a specific immune response, the need to suppress the recipient's immune system exists immediately. Rejection results from activation, differentiation, and proliferation of T-lymphocytes acting against donor cells that are recognized as foreign; the major determinants of which are cell surface markers known as human leukocyte antigens. Current immunosuppressive regimens and strategies are based on inhibition of this whole-cell response to foreign antigens.

Currently, most transplant centers use maintenance immunosuppression regimens including cyclosporine or tacrolimus, azathioprine or mycophenolate mofetil, and prednisone. In addition, in the first 2 wks post-transplantation, immunosuppression may be enhanced by the use of cytolytic agents such as $OKT_3$ (a monoclonal antibody to the $CD_3$ lymphocyte receptor), antithymocyte globulin (ATG), or new human derived IL2 receptor antibodies such as daclizumab.

A typical maintenance immunosuppressive regimen consists of cyclosporine 5 mg/kg twice daily (with dose adjusted to serum levels 250-350 ng/mL), azathioprine 1-2 mg/kg/day (adjusted to maintain a leukocyte count >4000-4500 $mm^3$) and prednisone approximately 0.5 mg/kg/day for the first 3 months tapered over the next 3 months to 15 mg/day and to 5 mg/day by the $12^{th}$ post-transplant month. Some programs have completely discontinued prednisone use after 1 yr or more following transplantation. Tacrolimus may be used in lieu of cyclosporine at a dose of approximately 0.1 mg/kg twice daily (adjusted to serum level 8-15 ng/mL), and mycophenolate mofetil 1-3 gm/day may be used in lieu of azathioprine.

All immunosuppressive drugs are wrought with complications, which can pose a significant problem following transplantation (Table 4). Cyclosporine and tacrolimus act by inhibiting IL2 gene transcription, thus decreasing T-lymphocyte activation and subsequent proliferation. Chronic nephrotoxicity is the most common complication of both agents and can develop in 25% to 75% of patients receiving these drugs, and to some degree in nearly 100% with long-term use. Acute renal toxicity is usually dose-related and typically reversible. In addition, other potentially nephrotoxic agents may be used in transplant patients including amphotericin B, trimethoprim-sulfamethoxazole, nonsteroidal anti-inflammatory agents, and aminoglycoside antibiotics which may compound the toxic effects of cyclosporine and tacrolimus. Both cyclosporine and tacrolimus are also associated with systemic hypertension, which can develop in up to 25% to 50% of lung transplant recipients. Hypercholesterolemia is also well described. The incidence of both post-transplant hypertension and hyperlipidemia may be lower with tacrolimus than cyclosporine. Other well described side-effects of tacrolimus and cyclosporine include neurologic toxicity such as tremors, paresthesias, headaches, confusion, depression, somnolence, seizures, white matter changes, coma, and death. Peripheral neurologic findings are also described. Neurotoxicity appears to be significantly more common with tacrolimus than with cyclosporine. Cyclosporine is also associated with hirsutism, gingival hyperplasia, and gastroparesis. Tacrolimus is associated with hyperglycemia and diabetes. Recently, both agents have

**Table 4**—*Immunosuppressive Drugs Used in Lung Transplantation*

| Drug | Common Adverse Effects |
|---|---|
| Cyclosporine | Nephrotoxicity, hypertension, neurotoxicity (tremor, seizures, headache), hyperlipidemia, hyperkalemia, hypomagnesemia, GI disturbance, hemolytic uremic syndrome, hirsutism, gingival hyperplasia |
| Tacrolimus | Nephrotoxicity, hypertension, neurotoxicity (tremor, seizures, headache), hyperlipidemia, hyperkalemia, hypomagnesemia, GI disturbance, hemolytic uremic syndrome, hyperglycemia, diabetes |
| Azathioprine | Leukopenia, macrocytic anemia, thrombocytopenia, hepatotoxicity, pancreatitis |
| Mycophenolate mofetil | Diarrhea, abdominal pain, nausea, leukopenia, anemia |
| Prednisone | Hyperglycemia, hypertension, hyperlipidemia, osteoporosis, myopathy, insomnia, cataracts, weight gain |
| $OKT_3$ | Cytokine release syndrome, hypotension, ARDS, aseptic meningitis |
| Antithymocyte globulin | Serum sickness, leukopenia, thrombocytopenia |

been reported to cause a hemolytic uremic syndrome or thrombotic thrombocytopenic purpura.

It is important that physicians taking care of transplant patients are aware of the numerous drug interactions with tacrolimus and cyclosporine. For example, the azoles result in a significant increase in cyclosporine and tacrolimus levels at the same dose. Likewise, discontinuation of azole agents without increasing the dose of cyclosporine or tacrolimus can result in an acute and life-threatening drop in therapeutic levels of these drugs. Interactions with macrolide antibiotics, calcium channel blockers, and gastric motility drugs are also reported. Levels of both agents are decreased with the use of rifampin or anticonvulsant agents.

Azathioprine inhibits nucleic acid synthesis and suppresses proliferation of lymphocytes. Toxicities of this drug include cytopenias such as leukopenia and thrombocytopenia. Macrocytic anemia can develop with chronic use. Pancreatitis and cholestatic hepatitis are well described with azathioprine use.

Mycophenolate mofetil also inhibits purine synthesis and blocks lymphocyte proliferation. Typical side-effects include gastrointestinal symptoms such as diarrhea, nausea, and abdominal pain. In addition, leukopenia and anemia are described.

Corticosteroids play a main role in post-transplant immunosuppression by binding to cytoplasmic glucocorticoid receptors, undergoing translocation into the nucleus, and then blocking cytokine transcription of genes and secretion from phagocytes. The side-effects of corticosteroid use are well known and include hyperglycemia, hypertension, hyperlipidemia, osteoporosis, proximal myopathy, mood disturbance, cataract formation, and weight gain.

The lympholytic agents such as $OKT_3$ and antithymocyte globulin act by depleting $CD_3$ lymphocytes by lysis, opsonization, and phagocytosis. Administration of $OKT_3$ may be associated with the cytokine release syndrome manifested by hypotension, noncardiogenic pulmonary edema, renal insufficiency, and aseptic meningitis. Antithymocyte globulin is associated with leukopenia, thrombocytopenia, and serum sickness. It should not be administered to those patients who have manifested allergic reaction to horse serum in the past.

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# Notes

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