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"//connect.facebook.net/en_US/all.js#xfbml=1"; fjs.parentNode.insertBefore(js, fjs);
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Significant advances in the treatment of pulmonary arterial hypertension have occurred in the last several years. The decision to refer a patient for transplantation requires a dynamic approach. Candidate selection and timing of referral to transplant centers is critical for success, particularly with current allocation protocols that do not take into account the severity of illness. Though long-term success is tempered by chronic allograft dysfunction and infection, considerable improvements in outcomes have established lung transplantation for pulmonary arterial hypertension as an efficacious and life-prolonging treatment. However, transplantation should be reserved for patients who have failed the best available medical therapy. Ideally, transplantation occurs when the clinically deteriorating patient has enough reserve to survive long enough to be transplanted but is not debilitated enough to jeopardize the graft. There is significant uncertainty with regard to this ideal.

The issue of who and when to refer for lung transplant evaluation is dynamic requiring a full understanding of the current medical management strategies and outcomes as well as current regional transplant waiting times and survival. In addition, individual patient characteristics may portend to worse medical outcome (eg, nonresponse to epoprostenol) or contraindicate transplantation altogether (HIV-associated pulmonary hypertension [PH]). Therefore, the challenge is to select those patients whose outcome will be improved by transplantation and whose individual characteristics will not result in heightened risk of graft loss. Transplantation should be reserved until it is expected to offer a survival advantage in those patients who have failed the best available medical therapy.

Guidelines have been published for candidate selection, which is similar among transplant centers (**Table 1**).

Table 1:

Pulmonary Arterial Hypertension Guidelines for Lung Transplantation

General Guidelines		Disease-specific Guidelines
Age Limits		Management
Single lung transplant	≥65 years	Treatment based on vasodilator challenge
Bilateral lung transplant	≥65 years	Vasodilator trial even in nonresponders
Heart-lung transplant	≥55 years	
Absolute Contraindications		Hemodynamic predictors of poor outcome on vasodilator
Creatinine clearance <50 mg/mL/min		Cardiac Index <2 liters/minute/m ²
HIV infection		Mean right atrial pressure >15 mm Hg
Active malignancy within 2 years*		Mean pulmonary artery pressure >55 mm Hg
Hepatitis B antigen positivity		
Hepatitis C with positive liver biopsy		Indications for transplant
Relative Contraindications		NYHA class III or IV on vasodilator
Symptomatic osteoporosis		Vasodilator nonresponder
Severe musculoskeletal disease		Intolerance to vasodilator
BMI >30		Patient preference
Hyperbilirubinemia >2.0 mg/dL		
Tobacco or substance abuse		
Psychosocial problems		
Invasive ventilator support		
Colonization with fungi or atypical mycobacteria		

*With the exception of basal cell and squamous cell carcinoma of the skin. Further, a 5-year waiting period is recommended for high stage renal, breast, and colon cancers as well as advanced melanoma (level III or greater).

Timing of Referral for Transplantation and Transplantation

The physician caring for the patient with pulmonary arterial hypertension (PAH) must be cognizant of 3 time-related variables: patient survival on current maximal medical management, approximate projected time on the waiting list, and patient survival after transplantation. Ideally, transplantation occurs when the clinically deteriorating patient has enough reserve to survive long enough to be transplanted but is not debilitated enough to jeopardize the graft. There is significant uncertainty with regard to this ideal.

The natural history of patients with primary pulmonary hypertension is a sobering 34% survival at 5 years.⁴ Though a regression equation has been derived to give prognostic information based on baseline hemodynamic variables (right atrial pressure, mean pulmonary artery pressure, and cardiac index), new medical therapeutics including calcium channel blockers,⁵ anticoagulation,^{5,6} prostacyclins,⁷⁻¹¹ and anti-endothelins¹² can alter prognosis significantly. Despite the lack of a predictive model, some guidelines are available.¹³⁻¹⁶ All patients who are NYHA class III and IV with refractory right ventricular failure on presentation should be referred for transplantation.¹⁷ Further, those who continue to have progressive right ventricular failure while on maximal medical therapy should also be referred at that time.¹⁸ Recent evidence from a prospective observational study¹⁹ demonstrates that patients on intravenous epoprostenol therapy and at first follow-up NYHA functional class has not improved to class I or II should be listed because their mortality at 3 years was 38% and 100% for NYHA class III and IV, respectively. Patients with NYHA class I and II limitation will likely have better survival on state-of-the-art medical therapy and referral should be deferred. However, patient characteristics with respect to blood type, size, and panel reactive antibodies should also be taken into account as these factors can significantly prolong time on the waiting list.²⁰

Until May 2005, the lung transplant allocation system did not take into account the acuity of illness.²¹ Using data obtained from all transplant centers reported to the United Network for Organ Sharing (UNOS), several variables were identified to affect mortality on the waitlist and post transplant (**Table 2**).

Table 2:

Data Elements Used in Determining the Lung Allocation Score

Diagnosis	Percent predicted FVC
Age	6-minute walk distance
NYHA Class	Serum creatinine
Assisted Ventilation	Pulmonary artery systolic pressure

	Diagnosis	Percent predicted FVC
BMI		Mean pulmonary artery pressure
Diabetes		Pulmonary capillary wedge mean
Supplemental Oxygen		

Adapted from UNOS. www.unos.org/resources/frm_LAS_Calculator.asp?index=97. Accessed March 18, 2010.

These variables are used to calculate a lung allocation score (LAS), which allows prioritization of candidates based on waitlist urgency and post-transplant survival. Using this new method, lung offers are made to candidates who are in most need of transplant and will receive greatest benefit.²² Waiting time has a limited role in the new lung allocation process. For candidates age 12 and older, it is used only as a tie-breaker between candidates with identical LAS. This is in contradistinction to candidates under age 12, where waitlist time plays a more significant role. Since the clinical introduction of lung transplantation, the number of potential recipients has far outpaced the number of donors. This donor shortfall had previously doubled the median time to transplant;²³ however, since the implementation of the LAS system, the number of active waitlisted lung candidates had a reduction in the mean waiting time from 792 days in 2004 to 141 days in 2007.²⁴ Similarly, the rate of death per 100 patient years also declined from a peak of 190.5 deaths in 1999 to 125.7 deaths in 2007.²⁴ Patient characteristics that can significantly prolong time on the waiting list are blood group antigen type, small patient size, and high panel reactive antibodies. The 1992-2001 UNOS registry demonstrated that blood type O patients waited on average 11 months longer than blood type AB patients.²¹ In addition, small patients, those with total lung capacity less than 4.5 L, wait an additional 60 days compared to recipients with total lung capacity greater than 4.5 L.²¹ Lastly, Appel et al demonstrated that patients with high levels of panel reactive antibodies also waited significantly longer for transplant and had higher mortality while waiting.²⁵ Though no guidelines exist regarding these issues, the authors' inclination is to refer class III and IV patients at the time of initial evaluation. If these patients exhibit a significant response to pulmonary vasodilator challenge, listing can be deferred. Functional class I and II patients are observed on maximal medical therapy until more significant right ventricular dysfunction develops. In the small group of patients with good functional status but with mitigating characteristics or history (ie, type O blood group or history of multiple previous transfusions), referral for listing is individualized and typically is reserved until some degree of disease progression has been demonstrated.

Type of Operation

Historically, treatment for PH required transplantation of a heart-lung block.²⁶ This initial approach was consequent to the concern that right ventricular function would not improve sufficiently to prevent perioperative morbidity and mortality.¹⁶ In the current era of surgical therapy for PAH, isolated lung transplantation is now used in most cases except in instances

where uncorrectable structural defects or left ventricular dysfunction is present in the native heart.^{16, 27} Considerable variations in practice patterns have been reported with respect to single vs bilateral lung transplantation for PH.¹⁴

In a retrospective study of the University of Pittsburgh's experience, both procedures result in similar length of mechanical ventilation, length of intensive care unit stay, and mortality.²⁸ Registry data from the International Society for Heart and Lung Transplantation (ISHLT) have confirmed no significant differences in survival in patients with PAH.²⁹ Despite no apparent differences in mortality, significant differences exist between those with single vs bilateral lung transplants with respect to blood flow, pulmonary artery pressure, and immediate cardiac index.

After single lung transplantation almost the entire cardiac output passes through the allograft while ventilation remains evenly distributed.³⁰⁻³³ This is well tolerated provided that minimal allograft dysfunction is present. In the face of reperfusion injury, infection, or rejection, significant hypoxia results from increased V/Q mismatch.^{32, 34}

Single lung recipient outcomes are inextricably linked to the function of the single allograft. Unlike other recipients transplanted for other reasons, these recipients have no functional reserve from their native lung because pulmonary blood flow continues to be preferentially shunted through the allograft despite ineffectual ventilation.¹⁶ Additionally, an occasional complication of single lung transplantation for PH is infarction of the native lung from hypoperfusion. Though rare, such situations require emergent re-exploration and pneumonectomy.

Bando and colleagues further explored the postoperative hemodynamic results following single lung, bilateral lung, and heart-lung transplantation in a cohort of 57 consecutive patients with pulmonary vascular disease. They demonstrated postoperative pulmonary artery pressures remaining significantly higher in those with single lung transplants than those with heart-lung or bilateral grafts; however, despite this difference, all groups experienced a significant decrease in pulmonary artery pressures. They further noted improvement in cardiac index in only the bilateral and heart-lung transplant recipients.³³

The superiority of bilateral vs single lung transplantation in patients with PAH remains a matter of debate. However, the majority of centers favor performing bilateral lung transplant for PH. In the ISHLT registry, less than 10% of transplants for PH were single lungs, with no single lungs reported in 2006. The authors prefer bilateral lung transplantation because it affords a greater reduction in pulmonary artery pressure, enhanced right ventricular protection, and a larger effective pulmonary reserve. In addition, recent investigations have demonstrated a significant survival advantage of bilateral lung transplantation in patients with end-stage lung disease.³⁵⁻³⁸

Perioperative Considerations

The patient with PAH has a significant propensity to aggravated right heart failure. Perioperative management requires the understanding of the multiple mechanisms that can

lead to progressive ventricular dysfunction, such as inadequate preload, provoked increases in pulmonary resistance, systemic hypotension, and hypoxemia.

Unlike other patients with other causes for end-stage lung disease, patients with PAH are at a higher risk of sudden death during exercise. In a self-perpetuating fashion, exercise-induced relative hypoxia increases pulmonary resistance, resulting in right ventricular pressure overload and failure.³⁹ If not remedied immediately, hemodynamic collapse and death result. However, there have routinely been patients with PAH who have participated in pulmonary rehabilitation with the caveat that adequate supplemental oxygen is administered to prevent systemic hypoxia and that heart rate is monitored and kept below 125.

Intraoperative management requires continuation of the optimized medical regimen through surgery because abrupt discontinuation can lead to profound pulmonary vasoconstriction, right heart failure, and death.⁴⁰ Typically, ascitic fluid is drained to allow for greater diaphragmatic excursion (sometimes requiring a temporary peritoneal catheter for intermittent decompression of the abdomen postoperatively). Additionally, the bypass is primed with fresh frozen plasma rather than isotonic crystalloid. Careful attention must be paid to volume status and diuretics must be used with caution based on hemodynamic monitoring. Prothrombin time, fibrinogen, and a thromboelastogram should guide replacement therapy intraoperatively. Oxygen saturation should be kept greater than 90% because hypoxemia causes pulmonary vasoconstriction.⁴¹ Normally, acidosis has minimal effect on pulmonary vascular resistance; however, in the presence of alveolar hypoxia its effect is considerably augmented. Rudolph et al have demonstrated a decrease in pulmonary vascular resistance in patients with PH by reducing the arterial carbon dioxide tension and hydrogen ion concentration.⁴² In the event that inotropic support is required in the face of euvoolemia, dobutamine is the first agent of choice due to its pulmonary vasodilatory properties.⁴³ Milrinone can also be used, but its lack of pulmonary specificity can aggravate systemic hypotension.⁴⁴ If hypotension continues, norepinephrine and phenylephrine can be used to augment coronary perfusion by maintaining systemic pressures.⁴⁵

Postoperative management can be quite challenging. Patients often die suddenly in the immediate postoperative period from hemodynamic perturbations, which are common in these patients. Although single and bilateral lung transplantation results in immediate afterload reduction in the operating room, right ventricular function recovers more slowly.^{27, 46-48} Care must be taken to avoid pulmonary vasoconstriction, and any therapy that decreases pulmonary vascular resistance should be weaned with caution.⁴⁰ Early extubation and mobilization of recipients and negative fluid balance are the cornerstones of management.

Loss of local defense mechanisms, consequent to denervation and reduction of mucociliary clearance,⁴⁹ identify why the allograft is more vulnerable to atelectasis and infection. Therefore, early extubation and mobilization of recipients augments lung re-expansion and recruitment alveoli. Fluids are restricted and diuretics administered to achieve a negative fluid balance.

Passive hepatic congestion from chronic right ventricular failure will likely have resulted in impaired liver synthetic function. Patients will be prone to coagulopathy and ascites. Intermittent drainage of ascites is indicated to augment ventilatory effort. Liberal use of vitamin K and fresh frozen plasma may be needed to prevent post-transplant coagulopathy.

Technique

For single lung transplants, the patient is positioned in lateral decubitus with access to the groin for possible cannulation. Entry into the chest via the fourth or fifth intercostal space from an anterolateral approach is our preference.

The recipient pneumonectomy requires intrapericardial dissection, division of the pulmonary artery at or beyond the take-off of the branch vessels, and the bronchus is divided immediately proximal to the upper lobe orifice. The use of the Endo GIA stapler facilitates the ligation and division of the pulmonary arteries and veins. After the lung is removed, the pericardium around the hilar structures is circumferentially incised. Mobilization of the pulmonary artery, pulmonary veins, and bronchus is maximized to facilitate anastomosis.

In patients with PAH, cardiopulmonary bypass is used routinely. However, through the use of nitric oxide and inotropic support, a number of patients have undergone sequential lung transplantation without bypass. The decision for cardiopulmonary bypass is made in cases where recipient hemodynamics, poor systemic perfusion, or technical factors dictate (eg, severe PH, concurrent intracardiac procedure, fragile or inadequate atrial cuff).

For patients undergoing bilateral transplants, the authors routinely use bilateral thoracosternotomy through the fourth intercostal space. Decisions regarding which side to implant first must take into account donor lung quality, native lung quality, and degree of technical difficulty.

Implantation is similar for left and right lung, though the left implantation is technically more difficult because the heart and left atrial appendage impede the exposure for the left atrial anastomosis. The recipient bronchus and donor bronchus are aligned, and the bronchial anastomosis is performed with a 4-0 polydioxanone suture (PDS) in running fashion. The orientation of the anatomy is preserved with membranous-to-membranous and cartilaginous-to-cartilaginous apposition with approximately one-ring intussusception. After completing the bronchial anastomosis, the stapled recipient pulmonary artery is occluded proximally with a Satinsky vascular clamp, and the staple line is trimmed away. The recipient pulmonary artery and donor pulmonary artery are aligned and anastomosed with 6-0 prolene suture in running fashion. Next a large Satinsky vascular clamp is placed on the body of the left atrium. The staple lines are excised and the orifices of the superior and inferior pulmonary veins are connected. An endothelial-to-endothelial anastomosis is created using a running suture of 5-0 prolene. Immediately before the 5-0 prolene suture is tied, the Satinsky clamp on the recipient left atrium is released to force out anterior residual air. Controlled, low-pressure reperfusion of the lung is achieved by gradually releasing the pulmonary artery clamp over 10-15 minutes.

Pleural spaces are well drained using chest tubes. Our preference is to use 24 Fr Blake tubes, as drainage is excellent and patient comfort is maximized. For single lung transplants, closure of the thoracotomy follows standard practice with complete drainage of anterior and posterior spaces. For bilateral transplants, the sternum is approximated using No. 5 wires, one simple set in the midline and one figure-8 on each side of the midline. The remainder of closure follows the same tenets as the standard thoracotomy. Lastly, the double lumen endotracheal tube is exchanged for a single lumen tube and fiberoptic bronchoscopy is

performed to assess the adequacy of the anastomosis and clear secretions.

Outcomes

Reported cumulative world experience exceeds 29,000 lung transplants with 79% 1-year and 52% 5-year overall survival.⁵⁰ Patients with PAH, idiopathic pulmonary fibrosis, and sarcoidosis have higher early mortality rates than other diagnoses.⁵⁰ For example, patients with cystic fibrosis have 1-, 5-, and 10-year survivals of 83%, 57%, and 40%, while those recipients with PAH have survivals of 71%, 52%, and 32%, respectively.⁵⁰ As mentioned previously, patients with PAH have the highest early hazard of all diagnoses. This can be explained by the requirement of cardiopulmonary bypass, and right ventricular dysfunction common in these patients, and the much higher incidence of severe primary graft dysfunction related to ischemia reperfusion injury. However, the conditional survival of those patients alive at 6 months post transplant is better in PAH patients than other diagnostic categories.

The 2 most common causes of death after the first transplant year include bronchiolitis obliterans and infection.⁵⁰ Long-term success of lung transplantation is limited by chronic allograft dysfunction—thought primarily due to chronic allograft rejection. This injury has been characterized by scar formation and fibrosis of the small airways and defined as bronchiolitis obliterans.⁵¹ The diagnosis of bronchiolitis obliterans requires a histopathologic specimen that includes the small- to medium-sized airways. However, transbronchial biopsies are insensitive for the diagnosis of bronchiolitis obliterans, since mostly alveolar tissues are obtained and bronchioles are infrequently sampled. The ISHLT developed a reproducible and reliable surrogate marker for bronchiolitis obliterans that utilizes declining FEV₁, the bronchiolitis obliterans syndrome.⁵² The system has been widely adopted and validated as a useful surrogate for histological bronchiolitis obliterans.

Bronchiolitis obliterans syndrome is the most common cause of morbidity and mortality following lung transplantation. At 5 years, 50% of transplanted patients have developed bronchiolitis obliterans syndrome and of the survivors, >33% continue to carry this diagnosis. Quality of life is significantly reduced once bronchiolitis obliterans syndrome develops, and the risk for death due to infection may also be increased.⁵³⁻⁵⁶

Kshetry and colleagues retrospectively analyzed 107 lung allograft recipients for the development of bronchiolitis obliterans to evaluate PAH as a potential risk factor. They demonstrated that patients with PAH developed bronchiolitis obliterans more often (39% vs 19%; $P=0.044$) and more rapidly (12 months vs 15 months; $P=0.05$) than those with other diagnoses.⁵⁷ However, results from other investigators have not corroborated these findings. Sundaresan at Washington University reported no significant tendency for development of bronchiolitis obliterans syndrome (surrogate for bronchiolitis obliterans) in patients with PAH.^{58, 59} At present there is no consensus as to whether PAH is a risk factor for the development of bronchiolitis obliterans.

Lungs seem particularly vulnerable to infection after transplantation. This is likely a consequence of a multiplicity of factors, including: constant exposure to potential pathogens, impaired local defense mechanisms (cough and mucociliary transport), and

immunosuppression. Transbronchial lung biopsy is an invaluable adjunct for diagnosing pulmonary infection, because clinical or physiological parameters are often difficult to distinguish.(60) Noncytomegalovirus pneumonia is most commonly caused by gram-negative bacteria and *Staphylococcus aureus* early in the postoperative period. Viruses, fungi, and protozoa comprise a set of more severe late infections that are more difficult to treat if prophylaxis is unsuccessful.(61)

Five years after transplantation, the most common morbidities excluding bronchiolitis obliterans include hypertension, hyperlipidemia, renal dysfunction, and diabetes (**Table 3**).

Table 3:

Common Morbidities 5 Years After Lung Transplantation

Outcome	Percentage
Hypertension	86.5%
Hyperlipidemia	43.4%
Renal dysfunction	38.3%
Abnormal creatinine <2.5 mg/dL	20.2%
Creatinine >2.5 mg/dL	13.7%
Dialysis dependent	3.4%
Renal transplantation	0.9%
Diabetes	27.8%

Adapted from Trulock.⁶²

Despite all these factors, more than 80% of 1-, 3- and 5-year survivors reported no activity limitations on follow-up. In addition, at 5 years, 40% of patients reported they are working full or part time.(62) Further, Gross and colleagues demonstrated significant improvement in health related quality of life and satisfaction in about 80% of recipients interviewed.(63)

Comment

Prior to the availability of epoprostenol, lung transplantation was indicated when mean right atrial pressure was >15 mm Hg, mean pulmonary artery pressure was >55 mm Hg, and cardiac index was <2 L/mim/m² and early survival was good. Subsequent to the availability of medical therapy, the indications for transplant have not changed but the patients are significantly more debilitated. Today, patients with PH have a significant early hazard with a 30-day survival of only 84% while patients with cystic fibrosis (CF) and chronic obstructive pulmonary disease (COPD) have a survival of 95% and 95%, respectively.⁵⁰ Based on a conditional survival of 3 months, there is no difference between PH, CF, and COPD each with a 6-month survival of 96%.⁵⁰ This high early mortality seen after lung transplantation in

patients with PH likely reflects the ability of vasodilator therapy to prolong life despite significant pathophysiology. Despite these sobering results, outcomes have improved since its original description and things must be kept in perspective.

With the significant medical advances in the treatment of PAH, transplantation should be reserved for those patients who have failed pharmacologic therapy. In this subset of patients who do not respond, deteriorate on, or do not tolerate pulmonary vasodilators, significant improvement in hemodynamics, NYHA functional class, actuarial survival, and quality of life has been demonstrated with isolated lung transplantation. Candidate selection and timing of referral to transplant centers is critical for ultimate success, particularly with current allocation protocols that do not take into account the severity of illness. Though long-term success is tempered by chronic allograft dysfunction and infection, significant improvements in outcomes have established lung transplantation for PAH as an efficacious and life-prolonging treatment.

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