Lung Transplant: Expanding Opportunities for Patients with Advanced Lung Disease

UPMC is one of the most recognized and experienced centers in the world for lung and combined heart-lung transplantation. Since the program’s inception in 1982, UPMC surgeons have performed more than 1,600 lung and heart-lung transplantations, far exceeding other transplant centers.

Our team of talented physicians continues to develop some of the most extensive clinical expertise in the field, giving hope to patients across the country and around the world. Recent developments include the use of conventional and ambulatory extracorporeal membrane oxygenation (ECMO) as a bridge to transplant, use of lobar transplants in patients with small thoracic volumes, and evolution of novel immunosuppression regimens.

Many factors thought previously to be contraindications to transplant, such as age greater than 65 and prior cardiac or thoracic surgery, are no longer prohibitive. Crucial to making life-transforming transplantation an option for more patients with advanced lung disease is early referral to allow sufficient time for risk mitigation and optimization of comorbidities. We are always happy to consult on cases and work with you to maximize options for your patients with progressive lung disease.

With great enthusiasm and respect,

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Advances in Lung Transplantation

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Lung transplantation has been an increasingly viable option for patients with end-stage lung disease. Beginning with the first successful human lung transplants at UPMC and the University of Toronto in the 1980s, more than 32,000 lung transplant procedures have been performed worldwide. Initial attempts at lung transplantation were limited by failure of bronchial anastomotic healing and high rates of rejection. With the advent of better immunosuppressive therapies, median survival has improved over time, from 4.0 years in 1988 to 1994 to 5.7 years in 2000 to 2008. At present, survival rates are 83.7% at one year, 67.0% at three years, 57.1% at five years, and 25.2% at 10 years. Patients experience an improvement in quality of life with more than 85% of patients having no activity limitations at one year post lung transplantation. More than 30% of patients maintain some type of active employment at five years after lung transplantation, despite some recipients who are 65 years or older at the time of transplantation.

Expanding recipient criteria
The number of lung transplant recipients is limited by the availability of suitable organ donors. Previously, the typical criteria of an ideal donor included age less than 55 years, mechanical ventilation less than 48 hours, normal chest x-ray, smoker status under 20 pack years, and pO2/FIO2 ratio above 300mg Hg.

In the last few years, large centers, including our program at UPMC, have shown that by liberalizing donor criteria, the availability of donor lungs could be significantly increased, without the loss of long-term favorable results. In addition, recipient criteria, such as age over 65 and the presence of coronary disease, were once considered to be contraindications for lung transplantation. However, carefully selected older individuals with limited comorbidities can have similar favorable outcomes after lung transplantation.

Our program often evaluates patients who have been declined for transplant at other centers for complex medical conditions. In particular, we have seen favorable outcomes in patients over the age of 70, patients with scleroderma, patients with coronary artery disease or valvular heart disease, cystic fibrosis patients who are colonized with resistant pathogens, and patients who require mechanical ventilation while waiting for transplant.

Organ allocation system changes
Due to the long waiting period and considerable mortality of pre-transplant patients waiting for transplantation, in 2005, a new organ allocation system was implemented in the United States. The new system allocates lungs on the basis of medical urgency and “net transplant benefit.” As a result, the death rate of listed patients, the median wait time, and the number of patients on the active waiting list declined as organs were no longer allocated based upon length of time on the waiting list. However, a larger number of patients are now more acutely ill prior to transplant, with more patients requiring ICU care just prior to lung transplantation. Mechanical ventilation and extracorporeal life support are now used as bridging strategies for transplantation. Extracorporeal membrane oxygenation (ECMO) historically has been used to support patients with severe primary graft dysfunction after transplantation, however its recent use to support patients with severe respiratory failure prior to lung transplantation has shown favorable results in regards to survival and risk of transplant-related morbidities.

Balancing immunosuppression risks and rejection
Traditional triple-drug immunosuppression, consisting of a calcineurin inhibitor (tacrolimus or cyclosporine), anti-metabolite, and high-dose corticosteroids, historically has had limited success in preventing acute rejection and other transplant-related complications. In fact, balancing the risk of rejection and adverse effects from immunosuppression often becomes problematic. As a result, newer therapies for immunosuppression and steroid-sparing strategies have evolved. Alemtuzumab, a monoclonal anti-CD52 antibody, allows for a low-dose steroid maintenance immunosuppressive regimen without the increased risk of both acute and chronic rejection when given as induction therapy at the time of lung transplantation. Despite the lower risk of rejection with alemtuzumab, there are no increased episodes of post-transplant lymphoproliferative disease suggestive of over-immunosuppression.

Lung Transplantation at UPMC
As the Lung Transplant Program at UPMC approaches 1,700 lung transplants over 30 years — including more than 600 transplants in the last six years, making it the most active program in the country during this time interval — lung transplantation remains the optimal therapy for appropriately selected patients with advanced respiratory failure, refractory to alternative medical or surgical therapies. The future is particularly bright, as active research is being conducted on immunosuppressive regimens, treatment regimens for allograft rejection, and enhancing the patient’s quality of life following lung transplantation.

Despite the relatively high cost to society, lung transplant recipients report an improvement in quality-of-life domains such as physical functioning, symptoms of dyspnea, and an overall greater satisfaction with their lives. Our ultimate goals are to maximize these quality-of-life measures, to reduce the severity and number of rejection episodes, to preserve lung function, and to improve long-term survival through better recognition and management of chronic rejection.

For information on how to refer a patient for lung transplantation, see Page 7.
Lung Transplant Outcomes Research: Contributing to Improved Care

By Cynthia Gries, MD
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Outcomes research seeks to understand the ultimate effect of health care practices and interventions. Knowledge gained from this type of research is used to help health care providers make informed decisions based on evidence and deliver the appropriate treatments to the right type of patients.

As an emerging field, outcomes research is particularly important in the field of lung transplantation. Although the first lung transplant was performed in 1963, the first lung transplant with long-term survival was not performed until 1983. Since then, roughly 22,000 lung transplants have been performed in the United States. As we gain more experience with lung transplantation, outcomes research has played an integral part in helping clinicians determine the most basic aspects of lung transplant medicine, such as approach to allograft preservation, surgical technique, or the importance of opportunistic infection prophylaxis.

Outcomes research also has helped identify risk factors of complications after lung transplantation, such as primary graft dysfunction, rejection, and bronchiolitis obliterans syndrome, in order to help inform patient decision-making and to identify future areas of research.

As one of the largest lung transplant centers in the country, UPMC has the potential to greatly contribute to outcomes research in the field of lung transplantation. In particular, our Transplant Patient Management System (TPMS) was designed as a patient tracking system and a research registry of all lung transplant and heart lung transplant patients transplanted at UPMC. TPMS has existed since 1989 and contains detailed pre- and post-transplant information on nearly 1,600 lung transplant recipients. In addition, it contains information on thousands of patients who were evaluated for lung transplantation at our center.

Following are highlights of ongoing lung transplant outcomes research in the UPMC Division of Pulmonary, Allergy, and Critical Care Medicine:

Impact of Low Health Literacy on Transplant Adherence and Long-Term Outcomes After Transplantation
Health literacy may play an important role in patient comprehension and adherence to the complicated medical regimen after lung transplantation. This study assesses the impact of health literacy on patient adherence and long-term outcomes, such as rejection, bronchiolitis obliterans, and death.

Impact of Donor-Specific HLA Antibodies on Bronchiolitis Obliterans After Transplantation
Donor-specific HLA antibodies (DSA) have been associated with poor outcomes after lung transplantation and may be related to the development of bronchiolitis obliterans syndrome (BOS). The primary goal of this study is to evaluate the relationship between DSA and freedom from BOS.

Outcomes of Lung Transplantation in Patients with Scleroderma
Due to the frequency of severe esophageal disease, lung transplantation of patients with scleroderma is controversial. Little data exists that helps define the risks and benefits of transplantation in this population and how to manage these patients postoperatively. UPMC currently has one of the largest populations of patients with scleroderma who have received a lung transplant. We are currently assessing early and late survival of these patients and investing the impact and management of severe esophageal dysmotility.

Pulmonary Hypertension and Mortality Risk After Lung Transplantation by Pretransplant Diagnosis
Pulmonary hypertension secondary to lung disease (PHLD) has been shown to be a predictor of severity of disease and mortality in patients awaiting lung transplantation. Little is known about the relationship of PHLD and posttransplant survival and how this may vary by disease. This study investigates whether pretransplant PHLD is associated with increased posttransplant one-year mortality in diagnostic groups of chronic obstructive pulmonary disease and cystic fibrosis.

Branching Out to Refine the Lung Allocation Score: Does Pretransplant Diagnosis Matter?
The Lung Allocation Score (LAS) was implemented in 2005 to balance waitlist urgency with transplant benefits. Criticism of the LAS has been that it poorly predicts survival and that misclassification of pretransplant diagnosis may be a contributing factor. The goal of this study is to assess the importance of pretransplant diagnosis in development of a three-year survival predictive model using pretransplant characteristics.
CASE PRESENTATION:
Airway Complications after Lung Transplantation

By Maria Crespo, MD, FCCP
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A 62-year-old woman underwent a double-lung transplant for end-stage lung disease due to pulmonary fibrosis in 2010. She received basiliximab for induction immunosuppression at the time of her transplantation.

Her post-transplant course was complicated by severe primary graft dysfunction requiring venovenous extra corporeal membrane oxygenation (ECMO) support, however her lung injury resolved over several days, and she was successfully weaned off ECMO support and extubated. At her first post-transplant bronchoscopy, she had severe airway ischemia reperfusion injury with no acute cellular rejection on transbronchial biopsies. The cultures grew Klebsiella, for which she received a two-week course of antibiotics.

She presented three weeks later with increased dyspnea, chest rattling, and cough. On exam, she had wheezing primarily over the right lung. Her pulmonary function test showed a decrease in her FEV1 and FEF 25–75%, and her flow volume loop showed a saw tooth appearance at the expiratory limb. Her chest CT scan with endobronchial reconstruction showed no pulmonary infiltrates and there was a significant stenosis at the right anastomosis (Image 1).

She underwent a bronchoscopy, which confirmed the severe stenosis seen on CT chest at the right anastomosis (Image 2). The patient had a balloon dilation procedure (Image 3 and Image 4) that resolved the stenosis (Image 5).

However, a few weeks later, she had recurrent symptoms, and a follow-up bronchoscopy revealed recurrent right anastomosis stenosis. A second balloon dilation was done and a hybrid covered stent was placed (Image 6). Her lung function improved and the bronchial stent was uneventfully removed one month later (Image 7).

Airway complications after lung transplantation were considered the “Achilles heel” for poor outcome after lung transplantation. In 1983 when the first lung transplants were performed, the incidence was as high as 80%. The improvement in graft preservation, donor/recipient selection, and surgical and medical advances has resulted in a lower rate of airway complications requiring treatment, in recent years 12% to 18% overall incidence. The mean duration from transplantation to the diagnosis and treatment of airway complications is 17 to 291 days. The most common airway complications seen are anastomotic dehiscence, which occurs very early after lung transplant, and stenosis. In contrast, malacia occurs much later from transplant.

The most common causes of airway complications after lung transplantation are airway ischemia reperfusion injury and primary graft dysfunction. Several other risk factors have been implicated in the development of airway complications after lung transplant, from surgical techniques (anastomosis type), donor-recipient factors (bronchial size discrepancies), infections (pre-transplant and post-transplant airway infections, particularly endobronchial aspergillosis) and medications (pre-transplant high-dose steroids and rapamycin).

Stenosis occurs mostly at the anastomosis, but patients may develop more distal segmental stenosis. The first treatment for significant stenosis (>50% luminal narrowing) is balloon dilation. Laser ablation is a treatment option for airway stenosis caused by granulation tissue.

Bronchial stents have been used for those patients who develop recurrent stenosis, as this patient did. We prefer to use the covered hybrid removable stents on this population to avoid the associated risks of granulation tissue and the high risk of airway colonization and infection associated with permanent stents. As demonstrated by this case, early airway complications often are successfully treated and permit a good outcome after lung transplant.
A 45-year-old female, with sarcoidosis was referred to UPMC for lung transplant evaluation. She had been declined by another center. There, she was found to be at high risk for development of invasive aspergillosis post-transplant due to the presence of bilateral pulmonary aspergillomas. As far as her underlying disease was concerned, she had stage IV sarcoidosis and had been on glucorticoids for a long time. Use of glucorticoid-sparing agents in the past had shown little to no success. Furthermore, she had developed bilateral apical cavity lesions with aspergillomas and had been on voriconazole for the last few years. In the past couple of years she had suffered two episodes of hemoptysis requiring embolization. A CT scan of the chest at our facility confirmed the presence of bilateral upper lobe cavities and large intracystic mycetomas (Image 1).

Over the past year, she has had progressive decline of her respiratory status with increased oxygen requirement. At UPMC, she underwent a full workup, which also included a thorough evaluation by transplant infectious disease experts. The treatment plan devised included continued use of voriconazole with an increase in dose to twice a day. Simultaneously, the dose of prednisone was weaned down. Additionally, at the time of transplant, an amphotericin irrigation of the chest wall was to be performed, and post-transplant inhaled amphotericin would be added to her treatment plan. The sputum cultures obtained during her visit grew Aspergillus fumigatus with minimal inhibitory concentration of $8 \mu g/mL$ for voriconazole, $1 \mu g/mL$ for posaconazole, $0.5 \mu g/mL$ for amphotericin B, and $0.25 \mu g/mL$ for caspofungin.

After a few discussions at our multidisciplinary lung transplant selection committee meeting, she was listed for a double-lung transplant. Unfortunately her condition worsened over the next few weeks and she was admitted to UPMC due to her increasing oxygen requirement. Following up on a complaint of sinus discomfort, a CT scan of the sinuses was obtained. It showed right anterior ethmoid and left sphenoid sinus opacification with central high-density material and erosion of the posteriorolateral left sphenoid wall suspicious for invasive aspergillosis.

An ENT consultation was obtained for further opinion. In light of her overall clinical situation, it was deemed too risky to subject her to general anesthesia with endotracheal intubation for sinus surgery. Her antifungal coverage was broadened to caspofungin, and inhaled amphotericin B deoxycholate (30 mg twice daily). And due to the high MIC of voriconazole, she was started on posaconazole (400 mg twice daily) instead of voriconazole.

In view of this new development, she was made inactive for a few days. She was later reactivated after detailed discussions at the candidate selection committee meeting. Fortunately, two days later, a suitable donor became available and she was semi-electively intubated. First she underwent left endoscopic sphenoidectomy with tissue removal and then left endoscopic total ethmoidectomy. A few hours later this was followed by double lung transplantation with cardiopulmonary bypass via bilateral anterolateral thoracotomies. Prior to implantation, the entire chest cavity was copiously irrigated with saline solution containing amphotericin. A separate solution containing caspofungin also was used to irrigate the entire chest cavity and recipient bronchial lumen. She tolerated the entire procedure well. Basiliximab was used for induction immunosuppression and she was maintained on a two-agent immunosuppressive regimen, namely tacrolimus and prednisone, post-transplant.

The pathology from sinus surgery revealed invasive fungal sinusitis and her explanted lungs showed findings consistent with sarcoidosis, as well as biapical aspergillomas (Image 2).

Post-operatively she was continued on posaconazole, caspofungin, and aerosolized amphotericin B 30 mg BID to finish a total of 12 weeks.

The patient is now 34 months post-transplant and has had no recurrence of invasive aspergillosis or airway complications. She continues to be free of any episodes of acute cellular rejection and is enjoying a good quality of life being back to work as a substitute teacher.

Dr. Haider wishes to acknowledge Lucio Mincs, MD, for contributing to this case presentation.

Image 1: CT image showing bilateral apical aspergillomas.

Image 2: Apical aspergilloma on gross pathology of explanted right lung.
Clinical Studies to Improve Lung Transplant Outcomes

Over the last three decades, early survival after lung transplant has improved, largely due to improvements in surgical techniques, early immunosuppression, and donor lung preservation. Further improvements in quality of life and survival will require an improved understanding and new treatments for primary graft dysfunction and chronic lung rejection, which manifests as bronchiolitis obliterans syndrome. UPMC transplant specialists are conducting several studies focused on lung transplant recipients:

Sodium Nitrite to Prevent Primary Lung Allograft Dysfunction: A phase 1b clinical trial is currently enrolling to determine the ability of sodium nitrite to prevent this early complication of lung transplant.

Novel Methods to Detect Early Bronchiolitis Obliterans: Physician investigators are performing a longitudinal observational study of novel chest CT methods using xenon washout and a non-invasive test of air trapping known as the Lung Clearance Index, to determine their ability to detect early chronic lung rejection non-invasively.

Impact of Hypogammaglobulinemia on Transplant Outcomes: In collaboration with immunologists in the division of Pulmonary, Allergy, and Critical Care Medicine at UPMC, transplant physicians are conducting a longitudinal observation study and an intervention study to determine the impact of hypogammaglobulinemia on rejection and infection after transplant, and the efficacy of immunoglobulin replacement therapy after lung transplant for prevention of transplant complications.

For more information about these research studies, contact the Cardiothoracic Transplantation Program at 412-648-6202 or cttransplant@upmc.edu.

How to Refer a Patient for Lung Transplant

To refer a patient for lung transplant evaluation, the following information is needed:

- Patient’s name and contact information
- Date of birth
- SSN
- Insurance information
- Medical records, including an H&P, PFT’s, CT scan, and CXR reports from the last two years, routine blood work results, current medication list, and any cardiac testing that has been done, such as an echo and/ or left- and right-heart catheterization.

The information can be faxed or mailed to the attention of Nancy Pepke, BSN, RN, CCTC, intake coordinator:

Fax: 412-648-6369
Mailing address: UPMC Presbyterian Lung Transplant Program 200 Lothrop St., Suite C-900 Pittsburgh, PA 15213

Insurance clearance can take up to two to three weeks. Once insurance authorization is received and medical records have been reviewed, the patient will be contacted for a phone interview/history. Once deemed acceptable for evaluation, the patient will be asked to provide a date when he or she AND a family member can come in for three to five days of testing. Referring physicians can request an expedited schedule for a patient based upon their assessment. If you have questions, please call the pretransplant office at 412-648-6202.

2012 Pitt Lung Conference Highlights

The 2012 Pittsburgh International Lung Conference (PILC) was held in October 2012 and proved to be one of the best and most well-attended conferences to date. Those who attended this informative two-day conference were able to expand their knowledge of A11/ARDS and related conditions. Following are some highlights:

- Day one focused on ARDS phenotypes, limitations of defining ARDS by phenotype, and the relationship of phenotype-to-disease outcomes; protocols for clinical management; and preclinical studies and endpoints in clinical trials. Speakers for these sessions included Drs. G. Rubenfeld, L. Gattinoni, B.T. Thompson, M. Mathay, R. Brower, P. Parsons, and D. Needham.


- A poster reception, following the scientific sessions on day one, provided an excellent forum for researchers to present their cutting-edge science. Winners of this year’s travel awards included B. Garibaldi (Johns Hopkins University), P. Tejera (Harvard School of Public Health), S. Roy (SUNY Upstate), N. Habashi (UMMS - R Adams Cowley Shock Trauma Center), M. Bhargava (University of Minnesota), S. Christley (University of Chicago), X. Lin (University of Rochester), K. Westphalen (Columbia University), A. Ghosh (SUNY Upstate Medical University), and J. Prezzano (SUNY Upstate Medical University).

- A banquet dinner featured a presentation by Derek C. Angus, MD, on the “Conundrum of Clinical Investigation in ARDS.”

Affiliated with the University of Pittsburgh School of Medicine, UPMC is ranked among the nation’s top 10 hospitals by U.S. News & World Report.
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UPMC is a $10 billion global health enterprise with more than 55,000 employees headquartered in Pittsburgh, Pa., and is transforming health care by integrating more than 20 hospitals, 400 doctors’ offices and outpatient sites, a health insurance services division, and international and commercial services. Affiliated with the University of Pittsburgh Schools of the Health Sciences, UPMC ranked No. 10 in the prestigious U.S. News & World Report annual Honor Roll of America’s Best Hospitals in 2012 — and No. 1 in Pennsylvania — with 15 adult specialty areas ranked for excellence. UPMC is redefining health care by using innovative science, technology, and medicine to invent new models of accountable, cost-efficient, and patient-centered care. For more information on how UPMC is taking medicine from where it is to where it needs to be, go to UPMC.com.

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At UPMC, pulmonologists are conducting a number of unique investigations that corroborate theories that heavy snoring and sleep apnea are contributors to cardiovascular disease.

Using Phenotypes to Evaluate and Manage Asthma
Physician researchers at the University of Pittsburgh Asthma Institute at UPMC are now using molecular and genetic information to identify asthma phenotypes and customize therapies in order to improve patient outcomes.

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