Lung Transplantation in 2015
past, present and future directions

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Historical Perspective

1963 - James Hardy performed first lung transplant
1976 - Cyclosporine introduced
1981 - Stanford performs first heart-lung transplant
1983 - Toronto performs first single lung transplant
1986 - Toronto performs first double lung transplant
First Lung Transplant: Hardy 1963

- Failure due to dehiscence of bronchial anastomosis
- At least 20 more attempts over next 20 years.
Reasons for Early Era Failures

- Poor patient selection
- Inadequate lung preservation
- Excessive immunosuppression
- Poor understanding of the physiology of the transplanted lung
- Limited donor availability
First Heart-Lung Transplant: Reitz 1982

Tracheal, Right Atrial, Aortic Anastomoses

Cyclosporine Immunosuppression

No Airway Problems
First Successful Isolated Lung Transplant: Cooper, 1983

- No Steroids for 10 days
- Cyclosporine Immunosuppression
- Omental Wrap around Bronchial Anastomosis
Background

• Ethical responsibility
  - to respect altruistic gifts and
  - to balance medical resource requirements of one potential recipient against those of others

• Concepts apply to listing and de-listing
Background

• Criteria for referral may differ from criteria for transplant
• Referral: individual patient & physician, desire for information
• Listing: when life expectancy is reduced
• Listing depends on organ allocation criteria
Indications

- Chronic, end-stage lung disease who are failing maximal medical therapy or no effective medical therapy exists
- Candidates – well informed, demonstrate adequate health behavior and compliant
- Primary goal – survival benefit
- Quality of life rather than curative treatment
Recipient Criteria

- Age < 75 years
- Medical therapy ineffective or unavailable
- Life expectancy <18 months
- Ambulatory with rehabilitation potential
- Acceptable nutritional status
- Adequate psychosocial profile and support
- No medical contraindications
General Contraindications

• Complex therapy with a significant risk of peri-operative morbidity and mortality
• Important to consider overall sum of contraindications and comorbidities
Absolute Contraindications

- Malignancy in last 2 years (exception cutaneous squamous and basal cell tumors)
  - 3-5 year disease free survival is prudent
  - Localized BAC??
- Significant dysfunction of other vital organs esp. liver, kidney, and CNS
- Significant CAD not amenable to PCI or CABG or associated with LV dysfunction
- Non-curable chronic active Hepatitis B, Hepatitis C, Hepatitis C infection w/ liver disease
- Significant chest wall/spinal deformity
Absolute Contraindications

• Active cigarette smoking active or within 6 months
• Drug or alcohol dependency active or within 6 months
• Untreatable psychiatric/psychological condition
• Noncompliance with medical management
• Absence of consistent or reliable social support system
Relative Contraindications

- Age?
- Critical or unstable clinical condition?
- Severely limited functional status with poor rehab potential
- Colonization with highly resistant or highly virulent bacteria, fungi or mycobacteria
- Severe obesity, BMI > 35 kg/m²
Relative Contraindications

• Mechanical Ventilation with need for profound sedation/paralysis impairing rehab or unstable state
• Severe Esophageal dysfunction
Diseases

• Usual disease states:
  - COPD/Emphysema
    • Alpha-1-antitrypsin deficiency
  - Idiopathic Pulmonary Fibrosis (IPF)/ Non-Specific Interstitial Pneumonia
  - Pulmonary Fibrosis associated with Collagen Vascular Disease
  - Cystic Fibrosis (CF)
  - Bronchiectasis
  - Pulmonary Arterial Hypertension (PAH)
  - Sarcoidosis
  - Lymphangioleiomyomatosis (LAM)
  - Pulmonary Langerhans Cell Histiocytosis (LCH)
Lung Transplant Options

Heart-Lung TX

Single Lung TX

Bilateral Sequential Lung TX
Living-Donor Lung Transplantation
For some retransplants, diagnosis other than retransplant was reported, so the total percentage of retransplants may be greater.
Adult Lung Transplants
Indications for Bilateral/Double Lung Transplants
(Transplants: January 1995 – June 2013)

For some retransplants, diagnosis other than retransplant was reported, so the total percentage of retransplants may be greater.
When Should Patients Be Referred?
Recipient Criteria
Timing of Evaluation

Emphysema

- FEV1 < 30%
- Hypoxia (chronic oxygen)
- Rate of Decline
- BODE Score
- Exceptions:
  - Hypercapnia
  - Secondary PH

- Also eval for LVRS
- Get them in rehab early
- Re-evaluate need for chronic steroids
Lung Transplant for COPD
Recipient Criteria

Timing of Evaluation

Pulmonary Fibrosis

• At diagnosis
• TLC < 60% predicted
• Hypoxia
• Rate of decline
Lung Transplant for IPF
Recipient Criteria

Timing of Evaluation

Cystic Fibrosis
- FEV1 < 30%
- pCO2 > 45
- Massive hemoptysis
- female
- Clinical Decline
  - weight loss
  - frequent exacerbations
  - resistant organisms
Cystic Fibrosis
• Pulmonary Infections
  ➢ Pan-resistant *Pseudomonas aeruginosa*
  ➢ *Burkholderia cepacia*
  ➢ Atypical mycobacteria
  ➢ *Aspergillus* sp.
• GI / Hepatic Disease
• Sinus disease
Lung Transplantation for Cystic Fibrosis
Recipient Criteria
Timing of Evaluation

Primary Pulmonary Hypertension

- NYHA III or IV
- Failed Prostacyclin infusion
- Hemodynamics: RAP > 15
  - CI < 2.0
  - Mean PAP > 60
Lung Transplantation for Primary Pulmonary Hypertension

Postoperative Hemodynamics and Ventilation after Single Lung Transplant for Pulmonary Hypertension

- Transplanted Lung: >90% Pulmonary Blood Flow, 50% Ventilation
- Native Lung: <10% Pulmonary Blood Flow, 50% Ventilation
Patients on Mechanical Ventilation

• Must be already fully evaluated and on the waiting list
• Must be stable
  ➢ Exclude significant non-pulmonary problems
  ➢ Exclude infection
  ➢ Nutritionally replete
  ➢ Weight bearing
• High Risk
Donor Operation

Who goes?
What do we do?
How long do we have?
Double-Lung Transplantation

Photos courtesy of Woo MS.
Post Operative Care
Just out of the OR…..

• Hemodynamics
  - Special considerations…..sepsis?

• Ventilator Nitric oxide
• Chest tubes
• Urine output etc…. 
PGD
Immediate Postoperative CXR
PGD
12 Hours Postoperative
Over the next couple days/weeks

- Bronchoscopy
- Extubation
- Chest tube management
- Immunosuppression
- Rehabilitation, feeding
- HOME
Immunosuppression
Immunosuppression

- **Preoperative**
  - Tacrolimus 0.05mg/kg oral 1 hours prior
  - Mycophenolate Mofetil 500 mg 1 hours prior

- **Intraoperative**
  - Methylprednisolone 15 mg/kg (when lung is reperfused)
Immunosuppression

- **Postoperative**
  - Tacrolimus 0.05mg/kg q 12 hours &
  - Mycophenolate Mofetil 250mg q 12 hours &
  - Methylprednisolone 125 q 8 hours x 48 hours then 1 mg/kg q 12 hours
  - Prednisone wean by 0.1-0.2 mg/kg/week until at 0.1 mg/kg/day
Infection Prophylaxis

• Viral
  • Valcyte C
  • Cytogam
  • CMV quant PCR each clinic visit and with any symptoms or admission
  • Flu vaccine for everyone

• Fungal
  • Itraconazole for life
  • Voriconazole if pre-op Aspergillus or Scedoporium
  • Inhaled Abelcet peri-op in house or with colonization

• PCP
  • Bactrim M, W, F or desensitization
Other Health Care Maintenance

- HMG-CoA Reductase
- Fosamax
- Anti-HT
- Advair
Rejection

- Acute
- Steroid Resistant
- Chronic
Clinical Signs / Symptoms

• Impossible to differentiate from infection
• New infiltrate / effusion
• Hypoxemia
• Dyspnea
• Cough, pleuritic chest pain
• Decreased FEV-1 or FEV 25-75%
Treatment of Rejection

Acute

- **Solumedrol 10mg/kg for 3 days**
- Treat the concomitant infection!
- Majority respond clinically to treatment
- Majority regain lost lung function
- Multiple early episodes predispose to chronic rejection
- Refractory/Steroid Resistant cases: photopheresis, thymoglobulin, rapamycin, plasmapheresis
Bronchiolitis Obliterans Syndrome

Definition (=chronic rejection)

Inflammatory disorder of the small airways of unknown etiology leading to their obstruction and destruction and eventually progressing to impairment of the large airways.
Treatment of Rejection
Chronic

• Switch IS medications
• Azithromycin
• Rapamycin
• Leflunomide
• Cytolytics
• Methotrexate
• Photopheresis
• Aggressively treat infectious processes
• Retransplantation
Survival and Functional Outcome
All pair-wise comparisons with CF were significant at $p < 0.0001$
Alpha-1 vs. COPD: $p < 0.0001$
Alpha-1 vs. IPF: $p < 0.0001$
COPD vs. IPF: $p < 0.0001$
IPF vs. IPAH: $p = 0.0362$

Median survival (years): Alpha-1 = 6.4; CF = 8.3; COPD = 5.5; IPF = 4.7; IPAH = 5.5; Sarcoidosis = 5.7
Adult Lung Transplants
Functional Status of Surviving Recipients
(Follow-ups: March 2005 – June 2013)
Future Directions
Challenges for the Future

- Recipient management/stabilization
- Expand Donor Pool
- Prevent/Treat Chronic Rejection
Single-site approach to venovenous ECMO cannulation:
A dual-lumen cannula is inserted in the internal jugular vein (extending through the right atrium and into the inferior vena cava). Venous blood is withdrawn through one “drainage” lumen with ports in both the superior and inferior vena cava. Reinfusion of oxygenated blood occurs through the second lumen, with a port situated in the right atrium. Inset: The two ports of the “drainage” lumen are situated in the superior and inferior vena cavae, distant from the reinfusion port. The reinfusion port is positioned so that oxygenated blood is directed across the tricuspid valve and directly into the right ventricle. This arrangement significantly reduces recirculation of blood when the cannula is properly positioned.
Transmedics (OCS)

- **Inspire Trial**
  - Site enrollment completed
    - FDA granted superiority petition
      - 10 completed
      - Primary endpoint change to “any” PGD 3

- **Expand Trial**
  - 5 cases completed!
Future Challenges
Chronic Rejection

• New immunosuppressive agents (sirolimus, monoclonal antibodies)

• Tolerance (permanent acceptance of the graft)
  ➢ Donor bone marrow infusion (mixed chimera)
  ➢ Blockade of T cell costimulatory pathways
Adult Lung Transplants
Kaplan-Meier Survival by Era
(Transplants: January 1990 – June 2012)

All pair-wise comparisons were significant at p <0.001

Median survival (years):
1990-1997: 4.1; Conditional = 7.0
1998-2004: 5.7; Conditional = 8.3
2005-6/2012: 6.1; Conditional = NA
Lung Transplantation Conclusions:

• Lung Transplantation can be an effective surgical therapy for end-stage pulmonary disease
• Huge progress made over last 10 years
• Donor shortage remains the overwhelming limitation
LUNG TRANSPLANT VOLUMES CALENDAR YEAR
2014: 5th BUSIEST PROGRAM IN THE NATION!

1. Duke University Hospital- 108
2. Cleveland Clinic Foundation- 104
3. The Methodist Hospital- 100
4. Univ of Pittsburgh Med Ctr- 86
5. St. Joseph’s Hospital and Medical Center-73
6. UCLA Medical Center-71
7. Barnes-Jewish Hospital-66
8. Indiana University Health-62
9. William P. Clements Jr. Univ Hospital-60
10. New York-Presbyterian/Columbia-59
PROGRAM HIGHLIGHTS

• Graft/Patient survival above national average:
  - 1 year survival ~ 90%
• Extremely short wait list times
  - Median Days on wait list 2014 = 12 days
• Shorter Length of Stays
  - Median post-op LOS 2014 = 13
• Age Limit
  - Upper age limit candidates on a case by case basis
• ECMO Program for “bridge” to transplant
• Predominant surgery is BILATERAL Lung Transplant
• Case by case evaluation for Re-transplants
Thank You!