Lung Transplant
A Physician and Patient Perspective

David Roe MD FCCP
Medical Director Lung Transplant and ECMO Program
IU Health Methodist Hospital
Objectives

• Review Indications for Lung Transplant
• Describe Transplant Process
• Review Outcomes of Lung Transplant
• Define Pulmonary Rehab Role in Lung Transplant Patients
• Discuss Patient Perspective
• Have fun, get needed CME, and don’t fall asleep....
Disclosure

• I have no relationships to disclose with any companies mentioned in this talk.
14th largest lung transplant center in United States

Lung transplants in 2010
39

Lung Transplants in 2011
41

Lung Transplants 2012
41
COPD and Rehab

GOLD Therapy at Each Stage of COPD

I: Mild
- FEV$_1$/FVC < 0.70
- FEV$_1$ ≥ 80% predicted

Active reduction of risk factor(s): influenza vaccination
Add short-acting bronchodilator (when needed)

II: Moderate
- FEV$_1$/FVC < 0.70
- 50% ≤ FEV$_1$ < 80% predicted

Add regular treatment with one or more long-acting bronchodilators (when needed):
Add pulmonary rehabilitation

III: Severe
- FEV$_1$/FVC < 0.70
- 30% ≤ FEV$_1$ < 50% predicted

Add inhaled glucocorticosteroids if repeated exacerbations

IV: Very Severe
- FEV$_1$/FVC < 0.70
- FEV$_1$ < 30% predicted or FEV$_1$ < 50% predicted plus chronic respiratory failure

Add long-term oxygen if chronic respiratory failure
Consider surgical treatments

Question...

- Which of the following is most effective for exercise performance in pulm rehab for COPD?
  - A. Strength Training
  - B. Growth Hormone
  - C. Inspiratory Muscle training.
  - D. High Intensity Exercise
  - E. Lunch Break
NOTE: This figure includes only the lung transplants that are reported to the ISHLT Transplant Registry. As such, this should not be construed as representing changes in the number of lung transplants performed worldwide.
AVERAGE CENTER VOLUME
Lung Transplants: January 1, 2000 - June 30, 2011

Average number of lung transplants per year

<table>
<thead>
<tr>
<th>Number of Centers</th>
<th>Average Center Volume</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-4</td>
<td>52</td>
</tr>
<tr>
<td>5-9</td>
<td>32</td>
</tr>
<tr>
<td>10-19</td>
<td>38</td>
</tr>
<tr>
<td>20-29</td>
<td>26</td>
</tr>
<tr>
<td>30-39</td>
<td>15</td>
</tr>
<tr>
<td>40-49</td>
<td>8</td>
</tr>
<tr>
<td>50+</td>
<td>7</td>
</tr>
</tbody>
</table>

Number of centers

Percentage of transplants

ISHLT

LUNG TRANSPLANTS

Transplant Recipient Age by Year of Transplant
(Transplants: January 1, 1987 – June 30, 2011)

Year of Transplant

- 0-11
- 12-17
- 18-34
- 35-49
- 50-59
- 60-65
- >65

Median recipient age (years)

% of Transplants

ISHLT

AGE DISTRIBUTION OF ADULT LUNG TRANSPLANT RECIPIENTS (1/1985-6/2011)

Recipient Age

% of Transplants

18-24 25-29 30-34 35-39 40-44 45-49 50-54 55-59 60-65 >65


ISHLТ
ADULT LUNG TRANSPLANTS
Kaplan-Meier Survival
(Transplants: January 1994 - June 2010)

Survival (%)

Survival (%)

Years

Survival (%)

Bilateral/Double Lung (N=19,566)
Single Lung (N=13,276)
All Lungs (N=32,842)

p < 0.0001

ISHLT

ADULT LUNG TRANSPLANTS
Indications for Single Lung Transplants
(Transplants: January 1995 - June 2011)

*Other includes:
Pulmonary Fibrosis, Other: 3.8%
Sarcoidosis: 1.9%
Bronchiectasis: 0.4%
Congenital Heart Disease: 0.3%
LAM: 0.9%
Connective Tissue Disease: 1.1%
OB (non-ReTx): 0.7%
Miscellaneous: 0.9%
ADULT LUNG TRANSPLANTS
Kaplan-Meier Survival by Diagnosis
(Transplants: January 1990 - June 2010)

HALF-LIFE: Alpha-1: 6.2 Years; CF: 7.5 Years; COPD: 5.3 Years; IPF: 4.4 Years; IPAH: 5.0 Years; Sarcoidosis: 5.3 Years

All comparisons with Alpha-1 and CF are statistically significant at < 0.05

COPD vs. IPF: p < 0.0001

ISHLT
All I ever needed to know about transplant I learned in…

The Three R’s of Transplant

The right lungs
  • Donor Selection
  • Matching (Panel reactive antibody)

The right time
  • Survival
  • Lung Allocation Score
  • PULMONARY REHAB

The right reason
  • Disease
Who are the players in the sandbox?

UNOS
- United Network for Organ Sharing
- private, non-profit organization that operates the Organ Procurement and Transplantation Network (OPTN) under a contract with the US Department of Health and Human Services.
- maintains data pertaining to the waiting list, organ matching, and transplants.

Organ Procurement Organizations
- OPOs are private, non-profit organizations that recover organs within their geographical territory and allocate them based on UNOS guidelines.
Players

• SRTR
  – Scientific of Registry Transplant Recipients
  – www.ustransplants.org
  – Large database of all centers
  – Can compare and contrast centers
  – Tracks outcomes used by CMS to help with accreditation

• Transplant Centers
Donor Selection

• One area of “art” of medicine

• Multiple factors are considered

• Relative and absolute contraindications

• High Risk Donors
Donor Physiology

Disruption in homeostatic regulation
  • Temperature dysregulation
  • Autonomic dysfunction

• Disturbances in endocrine function
  • Thyroid and Diabetes Insipidus

• Intense inflammatory reaction

• Aspiration / nosocomial pneumonia
Basic donor criteria

Age < 55 yr

ABO blood group compatibility

Clear chest radiograph

\[ P_{\text{ao}_2} \geq 300 \text{ mm Hg on fractional inspired oxygen of 1.0 and positive end-expiratory pressure 5 cm H}_2\text{O} \]

??pack-year smoking history

Gram stain shows sputum sample free of bacteria, fungus, and significant number of WBCs
Donor Management

• Manipulation of vent
  – Lung recruitment
  – ARDSnet strategy
  – Larger TV to increase volume??

• Hemodynamic monitoring and management

• Transfer of patients to IOPO
Chronic Obstructive Pulmonary Disease

- Emphysema, Chronic Bronchitis, Asthma
- 20 pts. with COPD are non-smokers (alpha-1)
- Occupational exposures
- FEV1/FVC < .70

Refer to Tx

- FEV1 < 25%
- PCO2 > 55
- Oxygen needs
- Pulmonary Hypertension
Variables and point values used for the computation of the body-mass index, degree of airflow obstruction and dyspnea, and exercise capacity (BODE) index*

<table>
<thead>
<tr>
<th>Variable</th>
<th>Points on BODE index</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0</td>
</tr>
<tr>
<td>FEV₁ (percent of predicted)</td>
<td>≥65</td>
</tr>
<tr>
<td>Distance walked in 6 minutes (m)</td>
<td>≥350</td>
</tr>
<tr>
<td>MMRC dyspnea scaleΔ</td>
<td>0-1</td>
</tr>
<tr>
<td>Body-mass index◊</td>
<td>&gt;21</td>
</tr>
</tbody>
</table>

* The cutoff values for the assignment of points are shown for each variable. The total possible values range from 0 to 10. FEV₁ denotes forced expiratory volume in one second.

• The FEV₁ categories are based on stages identified by the American Thoracic Society.

Δ Scores on the modified Medical Research Council (MMRC) dyspnea scale can range from 0 to 4, with a score of 4 indicating that the patient is too breathless to leave the house or becomes breathless when dressing or undressing.

◊ The values for body-mass index were 0 or 1 because of the inflection point in the inverse relation between survival and body-mass index at a value of 21.

Approximate 4 Year Survival Interpretation

- 3-4 Points : 67%
- 5-6 Points : 57%
- 7-10 Points : 18%

Interstitial Lung Disease

• IPF/UIP
  – Usual Interstitial Pneumonia
  – expansion of the interstitial compartment (that portion of the lung parenchyma sandwiched between the epithelial and endothelial basement membranes)

• Refer to Transplant
  – At diagnosis
  – FVC < 70%
  – DLCO < 50%
Diffuse parenchymal lung disease

- DPLD of known cause eg, drugs or association eg, collagen vascular disease
- Idiopathic interstitial pneumonias
- Granulomatous DPLD eg, sarcoidosis
- Other forms of DPLD eg, LAM, PLCH, etc.

- Idiopathic pulmonary fibrosis
- IIP other than idiopathic pulmonary fibrosis

- Desquamative interstitial pneumonia
- Acute interstitial pneumonia
- Nonspecific interstitial pneumonia (provisional)

- Respiratory bronchiolitis interstitial lung disease
- Cryptogenic organizing pneumonia
- Lymphocytic interstitial pneumonia
Cystic Fibrosis

Most common fatal autosomal recessive disease among Caucasian populations

persistent pulmonary infection, pancreatic insufficiency, and elevated sweat chloride levels

mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) protein, a complex chloride channel

Lung, Pancreas, Sinus

Lung Tx
- FEV1 < 30%
- Hemoptysis
- Malnutrition
- PCO2 > 50, PO2 < 55
Pulmonary Hypertension

- Mean pulmonary artery pressure greater than 25 mmHg at rest

The relationship between baseline mean pulmonary artery pressure (from less than 25 to more than 45 mmHg) and survival in patients with chronic obstructive pulmonary disease. Increasing pulmonary artery pressure was associated with a progressive decline in survival.

Redrawn from Bishop, JM, Prog Respir Res 1975; 5:9.
# Updated clinical classification of pulmonary hypertension (Dana Point, 2008)

1. Pulmonary arterial hypertension (PAH)
   1.1. Idiopathic PAH
   1.2. Heritable
      1.2.1. BMPR2
      1.2.2. ALK1, endoglin (with or without hereditary hemorrhagic telangiectasia)
      1.2.3. Unknown
   1.3. Drug- and toxin-induced
   1.4. Associated with
      1.4.1. Connective tissue diseases
      1.4.2. HIV infection
      1.4.3. Portal hypertension
      1.4.4. Congenital heart diseases
      1.4.5. Schistosomiasis
      1.4.6. Chronic hemolytic anemia
   1.5 Persistent pulmonary hypertension of the newborn

2. Pulmonary veno-occlusive disease (PVOD) and/or pulmonary capillary hemangiomatosis (PCH)

3. Pulmonary hypertension owing to left heart disease
   3.1. Systolic dysfunction
   3.2. Diastolic dysfunction
   3.3. Valvular disease

4. Pulmonary hypertension owing to lung diseases and/or hypoxia
   4.1. Chronic obstructive pulmonary disease
   4.2. Interstitial lung disease
   4.3. Other pulmonary diseases with mixed restrictive and obstructive pattern
   4.4. Sleep-disordered breathing
   4.5. Alveolar hypoventilation disorders
   4.6. Chronic exposure to high altitude
   4.7. Developmental abnormalities

5. Chronic thromboembolic pulmonary hypertension (CTEPH)

6. Pulmonary hypertension with unclear multifactorial mechanisms
   6.1. Hematologic disorders: myeloproliferative disorders, splenectomy
   6.2. Systemic disorders: sarcoidosis, pulmonary Langerhans cell histiocytosis: lymphangioleiomyomatosis, neurofibromatosis, vasculitis
   6.3. Metabolic disorders: glycogen storage disease, Gaucher disease, thyroid disorders
   6.4. Others: tumoral obstruction, fibrosing mediastinitis, chronic renal failure on dialysis

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ALK1: activin receptor-like kinase type 1; BMPR2: bone morphogenetic protein receptor type 2; HIV: human immunodeficiency virus.

Reproduced from: Simoneau, G., Robbins, IM, Boghetti, M, et al. Updated Clinical Classifications of Pulmonary Hypertension. J Am Coll Cardiol 2009; 54:S43. Illustration used with the permission of Elsevier Inc. All rights reserved.
Transplant Refer

- NYHA III-IV
- Cardiac Index < 2
- RAP > 15
- mPAP > 55mmHg
Recipient Selection

Initial screen with Pre-Tx Coordinator
Initial consult with transplant pulmonologist

Transplant Work-up
- Blood work, PFT’s, six minute walk, Info session
- CT scans, GB US, Cancer screening, Dentist
- R and L heart cath, V/Q scan, MUGA
- pH probe and esophageal manometry
- Social work, Dietary, Financial, Transplant Surgeon
- Lung measurements

Transplant Committee
Recipients

• 1. Maintain goal weight

• 2. Enroll in pulmonary rehab

• 3. Maintain pulmonary rehab

• 4. Social Support Structure
Contraindications

Uncontrolled or untreated pulmonary or extrapulmonary infection
Malignancy in the last two years
Significant dysfunction of other vital organs
Significant coronary artery disease or heart failure
Significant chest wall/spinal deformity
Active tobacco smoking
Drug or alcohol dependency
Unresolved psychosocial problems or noncompliance with medical therapy
HIV infection
Ongoing hepatitis B or C viral infection
Absence of a consistent or reliable social support system
Lung Allocation Score

Forced Vital Capacity
- Pulmonary Artery Pressure
- O2 requirements (L/min) at rest
- Age
- Body Mass Index
- Diabetes (IDDM)

- NYHA Classification
- 6’ walk test
- Ventilator use
- PCWP
- Creatinine
- Diagnosis
Sicker patients transplanted first

Less death on list awaiting transplant

Increase in transplants

More IPF
Post-Lung Transplant

Immediate Early Management:
- Extubation
- Chest Therapy
- Out of bed
- Ambulation
- Incentive spirometry
- Diet
- Immunosuppression
- Prophylaxis
- Thrombosis prophylaxis
- Peptic disease Prophylaxis
Out Patient follow-up

- Weekly for 6 weeks
- Bi weekly until 3 months
- Monthly for 12 months
- Every 3-4 months
- Labs, spiro, CXR
- Bronchoscopy
  - Surveillance
  - Clinically indicated
- Pulmonary rehab
Medications

Rejection
- Prograf
  - Tacrolimus
  - Calcineurin inhibitor

Prednisone

Cellcept
- Mycophenolate mofetil
- Cell cycle inhibitor

Rapamune
- Sirolimus

Imuran
- Azathioprine

Infection
- Bactrim
  - PCP
- Valcyte
  - CMV
- Vfend (Voriconazole)
  - Aspergillus
- Nystatin
  - Thrush
Signal transduction pathways involved in T cell activation

The provision of antigen specific, costimulatory, and cytokine signals leads to T cell activation. A number of pathways exist that transduce signals from the surface of the T cell to the nucleus. The end result of signal transduction is the transcription of mRNAs that code for a variety of pro-inflammatory proteins. The numbered steps depict sites at which various immunosuppressive agents act: 1, Cyclosporine; 2, Tacrolimus (FK506); 3, Rapamycin; 4, Corticosteroid.
## Immunosuppressive drugs: mechanisms of action and toxicities

<table>
<thead>
<tr>
<th>Drug</th>
<th>Description</th>
<th>Mechanism of action</th>
<th>Major toxicities</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cyclosporine</td>
<td>Cyclic peptide produced by the fungus <em>Tolyposcodium inflatum</em> gams</td>
<td>Inhibits IL-2 gene transcription, blunts T-lymphocyte activation and proliferation via inhibition of calcineurin</td>
<td>Nephrotoxicity, hypertension neurologic problems (tremor, headache, etc.), hirsutism, gingival hyperplasia</td>
</tr>
<tr>
<td>Tacrolimus (Prograf)</td>
<td>Macrolide lactone antibiotic isolated from the fungus <em>Strptomycyes tsukubaensis</em></td>
<td>Inhibits IL-2 gene transcription, blunts T-lymphocyte activation and proliferation via inhibition of calcineurin</td>
<td>Nephrotoxicity, hypertension, hyperglycemia, neurotoxicity</td>
</tr>
<tr>
<td>Sirolimus (Rapamune)</td>
<td>Macrocyclic triene antibiotic derived from <em>Strptomycyes hygroscopicus</em></td>
<td>Blunts T-lymphocyte activation via a non-calcineurin dependent pathway</td>
<td>Hypertension, hyperlipidemia, anemia, diarrhea, nephrotoxicity, pneumonitis</td>
</tr>
<tr>
<td>Azathioprine (Immunral)</td>
<td>Product of mercaptopurine, a purine antimetabolite</td>
<td>Inhibits DNA and RNA synthesis</td>
<td>Leukopenia, thrombocytopenia, nausea, vomiting, diarrhea, hepatotoxicity, pancreatitis</td>
</tr>
<tr>
<td>Mycophenolate mofetil (CellCept)</td>
<td>Fermentation product of <em>Penicillium species</em></td>
<td>Inhibits guanosine biosynthesis; blocks lymphocyte proliferation</td>
<td>Diarrhea, dyspepsia, leukopenia, anemia</td>
</tr>
<tr>
<td>Corticosteroids</td>
<td>Synthetic glucocorticoid</td>
<td>Blocks cytokine gene transcription and secretion from mononuclear phagocytes; possibly lyses T lymphocytes</td>
<td>Hyperglycemia, hypertension, osteoporosis, cataracts, myopathy, dyslipidaemia, mood disturbances</td>
</tr>
<tr>
<td>ATG or ALG (ATGAM)</td>
<td>Rabbit-derived polyclonal antibody to T cells</td>
<td>Depletes lymphocytes by lysis or by opsonization and phagocytosis; possibly modulates immune response in other ways</td>
<td>Leukopenia, thrombocytopenia, fever, allergic reactions to animal serum, serum sickness</td>
</tr>
<tr>
<td>OKT3 (Orthoclone OKT3)</td>
<td>Murine monoclonal antibody against CD3+ lymphocytes</td>
<td>Depletes CD3 lymphocytes by opsonization and phagocytosis; modulates T-cell interaction with antigen presenting cells</td>
<td>First-dose, cytokine-release syndrome, including hypotension or pulmonary edema, transient azotemia, leukopenia, septic meningitis</td>
</tr>
</tbody>
</table>

ATG: antithymocyte globulin; ALG: antilymphocyte globulin; OKT3: monoclonal antibody to CD3 complex of T-cell receptor.

Adapted from Trufek, EP, Am J Respir Crit Care Med 1997; 155:1789.
## Benefits of pulmonary rehabilitation in COPD

<table>
<thead>
<tr>
<th>Benefit</th>
<th>Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Improves exercise capacity</td>
<td>Evidence A</td>
</tr>
<tr>
<td>Reduces the perceived intensity of breathlessness</td>
<td>Evidence A</td>
</tr>
<tr>
<td>Can improve health-related quality of life</td>
<td>Evidence A</td>
</tr>
<tr>
<td>Reduces the number of hospitalizations and days in the hospital</td>
<td>Evidence A</td>
</tr>
<tr>
<td>Reduces anxiety and depression associated with COPD</td>
<td>Evidence A</td>
</tr>
<tr>
<td>Strength and endurance training of the upper limbs improves arm function</td>
<td>Evidence B</td>
</tr>
<tr>
<td>Benefits extend well beyond the immediate period of training</td>
<td>Evidence B</td>
</tr>
<tr>
<td>Improves survival</td>
<td>Evidence B</td>
</tr>
<tr>
<td>Respiratory muscle training is beneficial, especially when combined with general exercise training</td>
<td>Evidence C</td>
</tr>
<tr>
<td>Psychosocial intervention is helpful</td>
<td>Evidence C</td>
</tr>
</tbody>
</table>

Reproduced with permission from the Global Initiative for Chronic Obstructive Pulmonary Disease, based on an April 1998 meeting of the National Heart, Lung, and Blood Institute and the World Health Organization.
Impact of exercise training

Effect of exercise training on dyspnea compared with bronchodilators and oxygen.

Data from Am J Respir Crit Care Med 1999; 159:321.
D. High Intensity Exercise

- 60-80% of max work rate
- Endurance training of LE
- UE important as well
- Muscle training good but not most important
- Inspiratory muscle training good if muscle weakness PI max < 60 cm H20 and optimal medical therapy
Exercise after Transplant

- Evidence to support that a period of structured exercise training
  - improve maximal and functional exercise capacity
  - Improve skeletal muscle strength
  - Increase lumbar bone mineral density in lung transplant recipients
Rehab

• "bridging to transplant“
  – improving strength, endurance and mobility
  – intensive motivation and knowledge transfer can prepare patients as good candidates

• rehabilitation after LTx
  – regaining physical abilities and health related quality of life using the increased breathing capacities
COPD and Rehab

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Consider surgical treatments