An Update on Lung Transplantation: State of the Art 2013

Bryan A. Whitson, MD, PhD

Pulmonary Rehabilitation Conference 2013
February 26, 2013

Disclosures

- No conflicts of interest
- No financial relationships

Learning Objectives

- At the conclusion of this activity the participants should understand the indications for lung transplantation.
- At the conclusion of this activity, the participants should have a familiarity with the anticipated short and long term outcomes of a lung transplant recipient.
- At the conclusion of this activity, the participants should have an appreciation of the perioperative management of a lung transplant recipient.
- At the conclusion of this activity, the participants should have a familiarity with novel applications of extracorporeal circulation in patients with end-stage lung disease.

Imagine Being Out of Breath…

Successful Transplants Need a Team

Imagine Being Out of Breath…All The Time!
Lung Transplant History

- First performed June 11, 1963 by Dr. James D. Hardy (& Dr. Watts R. Webb) at the University of Mississippi
  - Carcinoma of left main stem bronchus
  - Azathioprine, prednisone and cobalt
  - Survived 18 days

Lung Transplant History

- The first heart-lung block was successfully performed by Drs. Norman E. Shumway and Bruce A. Reitz at Stanford on March 9, 1981.
  - Transplanted for pulmonary hypertension
  - Cyclosporin was key
  - Survived > 5 years

Lung Transplant History

- The first successful lung (single) transplantation was performed by Dr. Joel D. Cooper at the University of Toronto on November 7, 1983.
  - Pulmonary Fibrosis
  - Survived more than 7 years
  - Previously, early trouble had been airway dehiscence

Lung Transplant History

- The first successful double lung was performed by Cooper and Patterson at the University of Toronto in 1986.
  - The first double lung transplant for cystic fibrosis followed in 1988 at Washington University, St. Louis.
    - Two lungs needed due to infection

LUNG TRANSPLANTATION
Kaplan-Meier Survival by Recipient Age Group
(Transplants: January 1990 - June 2009)

Survival (%)

P = 0.0420

HALF-LIFE: Adult = 5.4 Years; Pediatric = 5.5 Years
Why Does One Get Transplanted

- Chronic Obstructive Pulmonary Disease (COPD) 35%
- Idiopathic Pulmonary Fibrosis (IPF) 15%
- Cystic Fibrosis (CF) 15%
- Primary Pulmonary Hypertension (PH) 10%
- Alpha-1 Antitrypsin Deficiency (alpha-1) 5%
- Bronchiectasis
- Sarcoidosis
- Other fibrotic and vascular diseases

PEDIATRIC LUNG TRANSPLANTATION: Indications (Transplants: January 1990 – June 2010)

<table>
<thead>
<tr>
<th>DIAGNOSIS</th>
<th>AGE: &lt; 1 Year</th>
<th>AGE: 1-5 Years</th>
<th>AGE: 6-11 Years</th>
<th>AGE: 12-17 Years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronic Fibrosis</td>
<td>11.7%</td>
<td>27.6%</td>
<td>36.7%</td>
<td>24.8%</td>
</tr>
<tr>
<td>Alveolar/Interstitial Fibrosis</td>
<td>12.0%</td>
<td>14.0%</td>
<td>22.0%</td>
<td>28.0%</td>
</tr>
<tr>
<td>Congenital Heart Disease</td>
<td>12.0%</td>
<td>10.5%</td>
<td>7.2%</td>
<td>1.8%</td>
</tr>
<tr>
<td>Recurrent Respiratory Infections</td>
<td>10.0%</td>
<td>4.0%</td>
<td>6.9%</td>
<td>6.9%</td>
</tr>
<tr>
<td>Other</td>
<td>14.0%</td>
<td>6.4%</td>
<td>4.5%</td>
<td>7.2%</td>
</tr>
</tbody>
</table>

Analysis includes living donor transplants

ISHLT

AGE DISTRIBUTION OF ADULT LUNG TRANSPLANT RECIPIENTS (1/1985-6/2010)

ADULT LUNG TRANSPLANTATION: Indications for Single Lung Transplants (Transplants: January 1995 - June 2010)

- Other includes:
  - Pulmonary Fibrosis, Other: 1.4%
  - Sarcoidosis: 1.9%
  - Bronchiectasis: 0.4%
  - Congenital Heart Disease: 0.3%
  - LAM: 0.8%
  - Connective Tissue Disease: 1.0%
  - Other: 0.6%
  - Miscellaneous: 0.3%
**Indications For Transplantation**

### Chronic Obstructive Pulmonary Disease
**Guidelines for Referral**
- **BODE index exceeding 5.**

<table>
<thead>
<tr>
<th>Variable</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
</tr>
</thead>
<tbody>
<tr>
<td>FEV1 (% predicted)</td>
<td>255</td>
<td>250-249</td>
<td>250-249</td>
<td>≤250</td>
</tr>
<tr>
<td>6-Minute Walk Test (meters)</td>
<td>350</td>
<td>250-349</td>
<td>150-249</td>
<td>≤150</td>
</tr>
<tr>
<td>MMRC Dyspnea Scale</td>
<td>0-1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Body Mass Index</td>
<td>&gt;21</td>
<td>&lt;21</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Guidelines for Transplantation**
- **BODE index of 7 to 10 or ≥1 of the following:**
  - Hospitalization for exacerbation (PaCO2 > 50 mm Hg).
  - Pulmonary hypertension and/or cor pulmonale despite O2-<30% predicted and either DLCO <20% or homogenous distribution of emphysema.

### Cystic Fibrosis and Other Bronchiectasis
**Guidelines for Referral**
- **FEV1 <30% predicted or a rapid decline in FEV1**, 
- **Exacerbation of pulmonary disease requiring ICU stay.**
- **More frequent exacerbations needing antibiotics**
- **Refractory and/or recurrent pneumothorax.**
- **Recurrent hemoptysis not controlled by embolization.**

**Guideline for Transplantation**
- **Oxygen-dependent respiratory failure.**
- **Hypercapnia.**
- **Pulmonary hypertension.**

### IPF and Non-Specific Interstitial Pneumonia
**Guideline for Referral**
- Histologic or radiographic evidence of UIP regardless of VC.
- Histologic evidence of fibrotic NSIP.

**Guideline for Transplantation**
- Histologic or radiographic evidence of UIP and (any below):
  - DLCO <35% predicted.
  - A > 10% decrement in FVC during 6 months of follow-up.
  - A decrease in pulse oximetry below 88% during a 6-MWT.
  - Honeycombing on HRCT (fibrosis score of > 2).
  - Histologic evidence of NSIP and any of the following:
    - DLCO < 35% predicted.
    - A > 10% decrement in FVC or 15% decrease in DLCO during 6 months.

### Pulmonary Arterial Hypertension
**Guideline for Referral**
- Persistent NYHA class III or IV on maximal medical therapy.
- Low (<350 meter) or declining 6-MWT.
- Failing therapy with intravenous epoprostenol, or equivalent.
- Cardiac index of less than 2 liters/min/m².
- Right atrial pressure exceeding 15 mm Hg.
Indications For Transplantation

In general, a potential recipient should be evaluated when their 2-3 year survival is < 50%

**ADULT LUNG TRANSPLANTATION**
Kaplan-Meier Survival By Diagnosis (Transplants: January 1990 – June 2009)

**ADULT LUNG TRANSPLANTATION**
Kaplan-Meier Survival by Procedure Type and Era (Transplants: January 1990 – June 2009)

Lung Transplant Surgery

**Ideal** Donor Selection
- Age <55 years
- ABO compatibility
- Clear chest radiograph
- PaO2 >300 on FIO2 = 1.0, PEEP 5 cm H2O
- Tobacco history <20 pack-years
- Absence of chest trauma
- No evidence of aspiration/sepsis
- No prior cardiopulmonary surgery
- Sputum gram stain—absence of organisms
- Absence of purulent secretions at bronchoscopy

**Lung Allocation Score**

![Graph showing Lung Allocation Score criteria](image-url)
Single Lung Transplant

Bilateral Sequential Lung Transplant

Bilateral Sequential Lung Transplant

Bilateral Sequential Lung Transplant
What do we worry about?

**Post Operative Concerns**

- Rejection
- Infection
- Primary Graft Dysfunction (PGD)
- Bleeding
- Right ventricular failure
- Nutrition
- Vasoplegia
- Airway dehiscence
- Mucous plugging
- Prolonged ventilation
- Bronchiolitis Obliterans
- Renal insufficiency
- Diabetes
- Gastroparesis
- Deep venous thrombosis
- Airway stenosis

**Bilateral Sequential Lung Transplant**

**What’s the worry?**

- Multi – organ system issues
- Evolution of concerns over time
- Contribute to morbidity and mortality

**ADULT LUNG TRANSPLANT RECIPIENTS: Cause Of Death**

(Deaths: January 1992- June 2010)

<table>
<thead>
<tr>
<th>CAUSE OF DEATH</th>
<th>0-30 Days (N = 2,204)</th>
<th>31 Days – 1 Year (N = 3,781)</th>
<th>&gt;1 Year – 3 Years (N = 3,425)</th>
<th>&gt;3 Years – 5 Years (N = 1,962)</th>
<th>&gt;5 Years – 10 Years (N = 2,336)</th>
<th>&gt;10 Years (N = 675)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BRONCHIOBLASTIC</td>
<td>1 (0.0%)</td>
<td>156 (4.2%)</td>
<td>164 (4.8%)</td>
<td>148 (4.5%)</td>
<td>133 (4.5%)</td>
<td>35 (5.2%)</td>
</tr>
<tr>
<td>ACUTE REJECTION</td>
<td>91 (4.2%)</td>
<td>79 (2.1%)</td>
<td>64 (1.9%)</td>
<td>53 (1.5%)</td>
<td>43 (1.7%)</td>
<td>8 (1.2%)</td>
</tr>
<tr>
<td>LYMPHOMA</td>
<td>1 (0.0%)</td>
<td>83 (2.2%)</td>
<td>87 (2.4%)</td>
<td>66 (1.9%)</td>
<td>62 (2.6%)</td>
<td>11 (1.6%)</td>
</tr>
<tr>
<td>MALIGNANCY, OTHER</td>
<td>2 (0.1%)</td>
<td>151 (4.0%)</td>
<td>164 (4.8%)</td>
<td>148 (4.5%)</td>
<td>133 (4.5%)</td>
<td>35 (5.2%)</td>
</tr>
<tr>
<td>CMV</td>
<td>0</td>
<td>96 (2.6%)</td>
<td>32 (0.9%)</td>
<td>6 (0.2%)</td>
<td>1 (0.1%)</td>
<td>0</td>
</tr>
<tr>
<td>INFECTION, NON-CMV</td>
<td>442 (20.1%)</td>
<td>1,334 (35.3%)</td>
<td>786 (22.9%)</td>
<td>374 (19.1%)</td>
<td>417 (17.9%)</td>
<td>120 (17.8%)</td>
</tr>
<tr>
<td>GRAFT FAILURE</td>
<td>619 (28.1%)</td>
<td>1,931 (51.2%)</td>
<td>1,384 (33.9%)</td>
<td>844 (44.1%)</td>
<td>607 (25.8%)</td>
<td>307 (45.5%)</td>
</tr>
<tr>
<td>CARDIOVASCULAR</td>
<td>238 (10.8%)</td>
<td>604 (16.0%)</td>
<td>560 (16.4%)</td>
<td>334 (17.2%)</td>
<td>257 (11.5%)</td>
<td>136 (19.9%)</td>
</tr>
<tr>
<td>OTHER</td>
<td>587 (26.4%)</td>
<td>819 (21.9%)</td>
<td>580 (16.5%)</td>
<td>280 (15.7%)</td>
<td>232 (10.0%)</td>
<td>66 (9.7%)</td>
</tr>
</tbody>
</table>

* ISHLT* 2011

*Heart Lung Transplant. 2011 Oct; 30(10): 1071-1132*
ADULT LUNG TRANSPLANT RECIPIENTS: Cause Of Death
(Deaths: January 1992- June 2010)

CAUSE OF DEATH 0-30 Days (N = 2,204)
31 Days – 1 Year (N = 3,781)
>1 Year – 3 Years (N = 3,425)
>3 Years – 5 Years (N = 1,962)
>5 Years – 10 Years (N = 2,336)
>10 Years (N = 675)

- BRONCHIOLITIS 7 (0.3%) 180 (4.8%) 870 (25.4%) 566 (28.8%) 572 (24.5%) 128 (19.0%)
- ACUTE REJECTION 81 (3.7%) 70 (1.9%) 55 (1.6%) 12 (0.6%) 18 (0.8%) 5 (0.7%)
- LYMPHOMA 1 (0.0%) 92 (2.4%) 67 (2.0%) 36 (1.8%) 58 (2.5%) 27 (4.0%)
- MALIGNANCY, OTHER 3 (0.1%) 112 (3.0%) 226 (6.6%) 180 (9.2%) 289 (12.4%) 78 (11.6%)
- CMV 0 98 (2.6%) 32 (0.9%) 6 (0.3%) 4 (0.2%) 1 (0.1%)
- INFECTION, NON-CMV 442 (20.1%) 1,334 (35.3%) 786 (22.9%) 374 (19.1%) 417 (17.9%) 120 (17.8%)
- GRAFT FAILURE 597 (27.1%) 655 (17.3%) 660 (19.3%) 364 (18.6%) 428 (18.3%) 111 (16.4%)
- CARDIOVASCULAR 239 (10.8%) 168 (4.4%) 141 (4.1%) 105 (5.4%) 122 (5.2%) 62 (9.2%)
- TECHNICAL 207 (9.4%) 94 (2.5%) 22 (0.6%) 11 (0.6%) 16 (0.7%) 9 (1.3%)
- OTHER 627 (28.4%) 978 (25.9%) 566 (16.5%) 308 (15.7%) 412 (17.6%) 134 (19.9%)

2011

Primary Graft Dysfunction (PGD)
- Ratio of arterial oxygen to inspired oxygen
- Over the first 72 hours
  - Grade 0 - PaO2/FiO2 >300 and normal CXR
  - Grade 1 - PaO2/FiO2 >300 and diffuse infiltrate
  - Grade 2 - PaO2/FiO2 between 200 and 300
  - Grade 3 - PaO2/FiO2 <200

Why Does PGD Matter?

Immunosuppression

- Calcineurin inhibitor
  - Inhibits IL-2 transcription and T-cell proliferation
  - Tacrolimus
  - Cyclosporine
- Anti-metabolite/purine synthesis inhibitor
  - T and B cell
  - Mycophenolate mofetil (MMF)
  - Azathioprine
- Steroid
ADULT LUNG RECIPIENTS
Maintenance Immunosuppression at Time of 1 Year Follow-up
Analysis limited to patients receiving prednisone

NOTE: Different patients are analyzed in each time frame.

ADULT LUNG RECIPIENTS
Induction Immunosuppression (Transplants: January 2002 - June 2010)
Analysis limited to patients receiving prednisone

NOTE: Analysis is limited to patients who were alive at the time of the follow-up.

ADULT LUNG RECIPIENTS
Induction Immunosuppression (Transplants: January 2000 - December 2009)
Analysis limited to patients receiving prednisone

PERCENTAGE OF ADULT LUNG TRANSPLANT RECIPIENTS
Experiencing Rejection between Transplant Discharge and 1-Year Follow-Up
Stratified by Type of Induction (Follow-ups: July 1, 2004 - June 30, 2010)

SURVIVAL BY INDUCTION USAGE
For Adult Lung Recipients (Transplants: April 1994-June 2009)
Conditional on survival to 14 days

Induction Immunosuppression?
Infectious Concerns

- Up to 35% of deaths are infectious in nature
- Consistent concern in patients with CF
  - "The most frequent cause of morbidity and mortality was acute pneumonia resulting from Pseudomonas cepacia"


Cystic Fibrosis Demographics

Bronchiolitis Obliterans Syndrome

- Irreversible decline in FEV1 of > 20% of baseline
  - BOS Grade 0: FEV1 > 80% of baseline
  - BOS Grade 1: FEV1 66% to 88% of baseline
  - BOS Grade 2: FEV1 51% to 65% of baseline
  - BOS Grade 3: FEV1 < 50% of baseline

FREEDOM FROM BRONCHIOLITIS OBLITERANS SYNDROME STRATIFIED BY DIAGNOSIS
For Adult Lung Recipients (Follow-ups: April 1994-June 2010)
Conditional on Survival to 14 days

Bronchiolitis Obliterans Syndrome – Denmark Group

Identify Patients At Higher Risk

- Low ejection fraction
- Previous myocardial infarction
- Redo cardiac surgery
- Pulmonary hypertension
- Renal dysfunction
- Urgent operations
- Coronary artery disease
- Structural heart defects
Perioperative - Evaluation
- Right heart catheterization
  - RA, PAS, PAD, PCWP, CO/CI
- Echocardiogram
- Arterial and mixed venous blood gases
- Coronary angiogram?

Indications For Transplantation

Pathophysiology of RV Failure & High PVR

Tidal Volume Extremes Increase PVR
- Low TV (e.g., atelectasis) extra-alveolar vessels narrow & collapse from smooth muscle and elastic fibers increases PVR
- High TV causes capillaries to stretch narrowing diameter and increasing PVR

Intraoperative PH Management
- Milrinone
- Inotrope
- Pulmonary vasodilators
- Inhaled NO and Epoprostenol
- Careful fluid management
- Avoid high PEEP - compress alveolar capillaries and elevate PVR
- Avoid hypoxia
- Go back on bypass
- Mechanical Circulatory Support / ECLS

Post-Operative Ventilator Management
- Minimize barotrauma
  - ↓ PIP
- Minimize atelectasis
- PEEP 8-10
- Low threshold for bronchoscopy
- Follow PaO2 / FiO2
Cardiac Risk Stratification

- 4% of candidates have significant coronary artery disease – regardless of age


Cardiac Risk Stratification

Risk of occult disease according to a semiquantitative coronary risk assessment:
- Age
- Gender
- Hypertension
- Hyperlipidemia
- Diabetes
- Smoking
- Family history of coronary artery disease
- Electrocardiographic abnormalities
- Echocardiographic abnormalities


High Lung Allocation Score

Log-rank p < 0.0001


High Lung Allocation Score and CF

Log-rank p < 0.001


Lung Transplants Off ECMO

Log-rank p < 0.0001

ECMO – YES
Retransplant - YES

ECMO – NO
Retransplant - NO

ECMO – YES
Retransplant - NO

ECMO – NO
Retransplant - YES

Hayes, Higgins, Kilic, Preston, and Whitson. Accepted at ATS 2013

What about ECMO as a bridge to lung transplant?
First Heart-Lung Machine Attempts

- John Gibbon
- Initial dog work in 1937
- Interrupted by WWII

Cross Circulation

Illustration of controlled cross-circulation as described by Gibbon Model II in 1954.

Where Are We Today?

Surgical Pioneer

Truly Bench-to-Bedside
Roller pump

- Hemolysis
- Constant flow

What is needed?

- Remove blood
- Return blood
- Oxygenate blood
- Hemodynamic support
- Decompress heart
- Stop heart?
- Be able to see

Centrifugal pump

- Preload dependent
- Afterload sensitive

Maquet Quadrox D

- Polymethylpentene
Perfusionists Are The Key

“Air goes in...air goes out...blood goes round and round.”

Brian Reinbold

ECLS – Arterio-Venous

Cardiohelp

28 Year Old Male Who Aspirates & ALI

ECLS – Veno-Venous

Various Configuration of ECMO / ECLS
**Bridge to Transplant - ECLS**

- Percutaneous V-V ECLS

**Bridge to Lung Transplantation and PH**

<table>
<thead>
<tr>
<th>Variable</th>
<th>1998-2005</th>
<th>2006-2010</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>In-hospital post-transplant mortality</td>
<td>3 (14)</td>
<td>10 (48)</td>
<td>0.0009</td>
</tr>
<tr>
<td>Abdominal sepsis</td>
<td>2 (9)</td>
<td>0</td>
<td>0.2</td>
</tr>
<tr>
<td>Extracorporeal life support</td>
<td>0</td>
<td>6 (29)</td>
<td>0.004</td>
</tr>
<tr>
<td>PA-LA Novalung</td>
<td>0</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>VA ECMO</td>
<td>0</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Endotracheal intubation</td>
<td>0</td>
<td>5 (25)</td>
<td>0.01</td>
</tr>
<tr>
<td>Wait time</td>
<td>5 (12)</td>
<td>0</td>
<td>0.03</td>
</tr>
<tr>
<td>Type of transplant</td>
<td>18</td>
<td>17</td>
<td>0.05</td>
</tr>
</tbody>
</table>

- University of Toronto
- 30-day post transplant mortality improved from 16.7% to 9.5%

**Surgery for Pulmonary Hypertension**

- Interventional Lung Assist for Pulmonary Hypertension
- Novalung
Surgery for Pulmonary Hypertension
- Novalung – University of Toronto

de Perrot et al. J Heart Lung Transplant 2011;30:987-992

We Need To Expand the Donor Pool
- In 2011 there were 1,822 lung transplants in the U.S.A.
- 17% conversion nationally
- In central Ohio, at Lifeline of Ohio, the local organ procurement organization, lung conversion rate was 18.8% in 2012

In 2011 there were 1,822 lung transplants in the U.S.A.
- 17% conversion nationally
- In central Ohio, at Lifeline of Ohio, the local organ procurement organization, lung conversion rate was 18.8% in 2012

Perfusion Catches Public Attention
- Alexis Carrel – Nobel laureate
- Charles Lindberg – aviator
- Perfused a cat thyroid
  - April 5, 1935
  - 18 days

Expanding The Donor Pool

Expanding The Donor Pool

Expanding The Donor Pool

Expanding The Donor Pool
Expanding The Donor Pool

<p>| | | | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>


Developing the OSU Lung

Miniatrized Organ Perfusion

Summary

- COPD, ILD/IPF, and CF are the most frequent indications for lung transplantation
Summary

- COPD, ILD/IPF, and CF are the most frequent indications for lung transplantation
- Immediate infections concerns shift to rejection concerns long term
- Multi-organ system, multi-provider team approach to optimize outcomes

Acknowledgements

- Drs. Higgins, Kilic & Black
- Drs. Pope-Harman, Kirkby, & Hayes
- Drs. Crestanello, Sai Sudhakar, & Sirak
- OSUWMC Ross Perfusionists & OR Staff
- Drs. Papadimos, Tripathi, Flores, Essandoh & Andritsos
- Staci Carter, Tina DeVoe, Susan Graff, & Jody Knisley
- Many many others...

Remember...

Be a Buckeye for Life
Support Organ and Tissue Donation