Lung Transplantation in 2016

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The Ohio State University Pulmonary Rehabilitation Conference

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Disclosures

- No conflicts of interest
- No financial relationships
Goals

- History and Outcomes in lung transplant
- Which patients may benefit
- Transplant workup and listing
- Primary care and transplant patients
- More on the horizon
Patient “Cindy”

63 yo woman
Emphysema diagnosed 5 years ago
Hypertension, Anxiety
Hospitalized once for her emphysema over the holidays
Quit smoking when she came into the hospital
FEV1: 21% by current spirometry

How many think she could be a candidate for transplant listing?
Lung Transplant

History and Survival

Indications-Referral -Workup

Transplant Coordination

Aftercare of Transplant Patients

On the Horizon
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

Reitz BA. JTCVS 2011;141:867-9
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
International Lung Transplants

Number of transplants

- Bilateral/Double Lung
- Single Lung
Adult Lung Transplant Survival
(Transplants: January 1994 – June 2011)

Median survival (years):
Double lung: 6.9; Conditional = 9.6
Single lung: 4.6; Conditional = 6.5
All lungs: 5.6; Conditional = 7.9
History and Survival

Indications-Referral - Workup

Transplant Coordination

Aftercare of Transplant Patients

Miracles on the Horizon
Who Gets Transplanted?

Chronic Obstructive Pulmonary Disease (COPD) 33%
Pulmonary Fibrosis (PF) 27%
Cystic Fibrosis (CF) 17%
Primary Pulmonary Hypertension (PH) 10%
Alpha-1 Antitrypsin Deficiency (Alpha-1) 6%
Bronchiectasis
Sarcoidosis
Other fibrotic and vascular diseases

J Heart Lung Transplant 2013
Indications For Transplantation

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

<table>
<thead>
<tr>
<th>DIAGNOSIS</th>
<th>SLT (N = 12,339)</th>
<th>BLT (N = 18,334)</th>
<th>TOTAL (N = 30,673)</th>
</tr>
</thead>
<tbody>
<tr>
<td>COPD/Emphysema</td>
<td>5,769 (46.8%)</td>
<td>4,839 (26.4%)</td>
<td>10,608 (34.6%)</td>
</tr>
<tr>
<td>Idiopathic Pulmonary Fibrosis</td>
<td>3,995 (32.4%)</td>
<td>2,938 (16.0%)</td>
<td>6,933 (22.6%)</td>
</tr>
<tr>
<td>Cystic Fibrosis</td>
<td>214 (1.7%)</td>
<td>4,941 (26.9%)</td>
<td>5,155 (16.8%)</td>
</tr>
<tr>
<td>Alpha-1</td>
<td>728 (5.9%)</td>
<td>1,225 (6.7%)</td>
<td>1,953 (6.4%)</td>
</tr>
<tr>
<td>Idiopathic Pulmonary Arterial Hypertension</td>
<td>78 (0.6%)</td>
<td>894 (4.9%)</td>
<td>972 (3.2%)</td>
</tr>
<tr>
<td>Pulmonary Fibrosis, Other</td>
<td>424 (3.4%)</td>
<td>537 (2.9%)</td>
<td>961 (3.1%)</td>
</tr>
<tr>
<td>Bronchiectasis</td>
<td>50 (0.4%)</td>
<td>815 (4.4%)</td>
<td>865 (2.8%)</td>
</tr>
<tr>
<td>Sarcoidosis</td>
<td>236 (1.9%)</td>
<td>547 (3.0%)</td>
<td>783 (2.6%)</td>
</tr>
<tr>
<td>Re-Transplant: Obliterative Bronchiolitis</td>
<td>253 (2.1%)</td>
<td>219 (1.2%)</td>
<td>472 (1.5%)</td>
</tr>
<tr>
<td>Connective Tissue Disease</td>
<td>127 (1.0%)</td>
<td>232 (1.3%)</td>
<td>359 (1.2%)</td>
</tr>
<tr>
<td>Obliterative Bronchiolitis (Not Re-Transplant)</td>
<td>80 (0.6%)</td>
<td>237 (1.3%)</td>
<td>317 (1.0%)</td>
</tr>
<tr>
<td>LAM</td>
<td>101 (0.8%)</td>
<td>207 (1.1%)</td>
<td>308 (1.0%)</td>
</tr>
<tr>
<td>Re-Transplant: Not Obliterative Bronchiolitis</td>
<td>127 (1.0%)</td>
<td>162 (0.9%)</td>
<td>289 (0.9%)</td>
</tr>
<tr>
<td>Congenital Heart Disease</td>
<td>43 (0.3%)</td>
<td>224 (1.2%)</td>
<td>267 (0.9%)</td>
</tr>
<tr>
<td>Cancer</td>
<td>6 (0.0%)</td>
<td>26 (0.1%)</td>
<td>32 (0.1%)</td>
</tr>
<tr>
<td>Other</td>
<td>108 (0.9%)</td>
<td>291 (1.6%)</td>
<td>399 (1.3%)</td>
</tr>
</tbody>
</table>
AGE DISTRIBUTION OF ADULT LUNG TRANSPLANT RECIPIENTS (1/1985-6/2010)
### Proportion of CF Transplants Increases

<table>
<thead>
<tr>
<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>1</td>
<td>5</td>
<td>167</td>
<td>775</td>
</tr>
<tr>
<td>1.2%</td>
<td>4.5%</td>
<td>56.0%</td>
<td>71.7%</td>
</tr>
</tbody>
</table>

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

*Other includes:
- Pulmonary Fibrosis, Other: 3.4%
- Sarcoidosis: 1.9%
- Bronchiectasis: 0.4%
- Congenital Heart Disease: 0.3%
- LAM: 0.8%
- Connective Tissue Disease: 1.0%
- OB (non-ReTx): 0.6%
- Miscellaneous: 0.9%
Single Lung Transplant
ADULT LUNG TRANSPLANTATION: Indications for Bilateral/Double Lung Transplants (Transplants: January 1995 - June 2010)

*Other includes:
- Pulmonary Fibrosis, Other: 2.9%
- Sarcoidosis: 3.0%
- Bronchiectasis: 4.4%
- Congenital Heart Disease: 1.2%
- LAM: 1.1%
- Connective Tissue Disease: 1.3%
- OB (non-ReTx): 1.3%
- Miscellaneous: 1.7%
Bilateral Sequential Lung Transplant
Bilateral Sequential Lung Transplant
Bilateral Sequential Lung Transplant
Bilateral Sequential Lung Transplant
Bilateral Sequential Lung Transplant
Bilateral Sequential Lung Transplant
Survival comparisons
All comparisons with Alpha-1 and CF are statistically significant at < 0.01

COPD vs. IPF: p < 0.0001

ISHLT 2011
ADULT LUNG TRANSPLANTATION
Kaplan-Meier Survival by Procedure Type and Era
(Transplants: January 1990 – June 2009)
Diagnosis: Cystic Fibrosis, Double Lung

Survival comparisons
1990-1994 vs. 1995-1999: p = 0.0312
1990-1994 vs. 2000-6/2009: p < 0.0001
1995-1999 vs. 2000-6/2009: p = 0.0091

CF/Double lung/1990-1994 (N=507)
CF/Double lung/1995-1999 (N=1,020)

N=24
N=244
N=128

ISHLT 2011
THE OHIO STATE UNIVERSITY
WEXNER MEDICAL CENTER
Transplant “Window”

Between the time the patient is sick enough to benefit from transplant--
- Longer life
- Better quality of life
-- And not too ill to get through the procedure safely

Window can be long for some diseases—We may begin seeing patients long before listing

Window can open with some interventions
(Rehab, nutrition, treatment of infections)
Let’s Talk About COPD: When to send your patients

- FEV1 < 25% predicted
- BODE index exceeding 5

<table>
<thead>
<tr>
<th>Variable</th>
<th>Points on BODE Index</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>FEV1 (% predicted)</strong></td>
<td>0 1 2 3</td>
</tr>
<tr>
<td>≥65</td>
<td>50-64</td>
</tr>
<tr>
<td>6-Minute Walk Test (meters)</td>
<td>≥350</td>
</tr>
<tr>
<td>MMRC Dyspnea Scale</td>
<td>0-1</td>
</tr>
<tr>
<td>Body Mass Index</td>
<td>&gt;21</td>
</tr>
</tbody>
</table>
What do we look for when we list for COPD?

BODE index of 7 to 10 or ≥1 of the following:
Hospitalization for exacerbation
  PCO2 > 50 mm Hg during hospital stay
Pulmonary hypertension and/or cor pulmonale despite O2
FEV1 < 20% and either
  -DLCO < 20% or
  -Homogenous distribution of emphysema
Referring patients with Pulmonary Fibrosis

Histologic or radiographic evidence of UIP regardless of Vital Capacity
Histologic evidence of fibrotic NSIP

Window can be variable in Fibrosis patients

When we *list* patients with Pulmonary Fibrosis

**Histologic or radiographic evidence of UIP and (any below):**
A DLCO <39% 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:**
A DLCO < 35% predicted.
A > 10% decrement in FVC or 15% decrease in DLCO during 6 months
Referrals for Patients with CF

$\text{FEV}_{1} < 30\%$ predicted or a rapid decline in $\text{FEV}_{1}$
Exacerbation of pulmonary disease requiring ICU stay
More frequent exacerbations needing antibiotics
Refractory and/or recurrent pneumothorax
Recurrent hemoptysis not controlled by embolization

Window varies, but deteriorations can be very acute

Listing CF Patients

Increasing hospital stays
Increasing exacerbations
Increasing bleeds
Oxygen-dependent respiratory failure
Hypercapnia
Pulmonary hypertension
Referral for Pulmonary Hypertension

NYHA functional class III or IV, irrespective therapy
Rapidly progressive disease

Window may vary depending on response to treatment and other factors

Listing Patients with Pulmonary Hypertension

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
### Lung Transplant isn’t for everyone

**POTENTIAL CONTRAINDICATIONS TO LUNG TRANSPLANT**

**Because Lung Transplant may be too risky or may not fix the problem:**
- Significant systemic or multi-system disease
  - Infections
    - (HIV, Hepatitis, Burkholderia, mycobacteria, fungus)
- Renal disease
- Cardiac disease
- Cancer within last two years
  - (aside from non-melanoma skin cancer)
- Some programs have age limits
- Ventilator dependence
- BMI greater than 35 or less than 17
- Significant debility (should be able to rehab)

**Because the surgery may not be technically feasible:**
- Previous cardiac or Thoracic surgery
- Thoracic deformities

**Because of After-Transplant risk:**
- Chronic pain or narcotic abuse
- Current tobacco use (minimum of six month abstinence)
- Active drug or alcohol dependence
- Major psychiatric illness
- Symptomatic osteoporosis
- Corticosteroid therapy, greater than 20mg daily
Let’s take another look at Cindy

63 yo woman
Emphysema diagnosed 5 years ago
Hypertension, Anxiety
Hospitalized once for her emphysema over the holidays
Quit smoking when she came into the hospital
FEV1: 21% by current spirometry
Just started Pulmonary rehab
Referral Process

The referral process should provide an open door to appropriate patients
- Easy for referring HCPs
- Minimal pre-screening
- Help referring HCPs manage their patients
- Avoid undermining HCP esteem in patients’ eyes
- Allow HCPs to remain engaged with their patients
Referral Process

Patients who may qualify for lung transplant listing make up only a small part of the average Pulmonologist’s practice.

Insurance approval is required to go forward with workup (Can create delay)

Only 1 in 10 referrals turn out to be candidates for listing.
Pre-Transplant workup

**Extensive**
Determine candidacy, quantify and optimize underlying conditions, meet team members.

**Pre-Screening:** Smoking, debility, weight, major medical contraindications

**Tier 1:**
Disease staging, identify major contraindications and modifiable contraindications:
- PFTs
- Basic Imaging: CXR, CT Chest, Quantitative VQ, Echocardiogram
- Basic Labs
- Visits: SW, Pulmonology

*Potentially modifiable contraindications:*
(If disease progression allows sufficient time)
- Weight / nutritional deficiency
- Substance use
- Physical conditioning

**Tier 2:**
Additional identification of contraindications, identify factors impt in transplant process:
- R & L Heart Cath
- Serology, Tissue typing
- Visits: Cardiothoracic Surgeon, ID, Palliative Care
It’s all complicated…

*HCP communication is important:*

“Let’s see if transplant could be a treatment for your disease”

Rather than

“You absolutely need a lung transplant.”

“I’m sending you to Medical Center X to get one tomorrow.”
Lung Transplant

History and Survival

Indications-Referral -Workup

Transplant Coordination

Aftercare of Transplant Patients

On the Horizon
Listing is a Process too

Patient Selection Committee—center-based
Ohio Solid Organ Transplant Consortium
Insurance approval for transplant
Entry process in UNET—
  Allows for calculation of Lung Allocation Score, preference of laterality or bilateral lungs, ABO, and preferred size range of donor
Lung Transplant Surgery

Donor Factors

Recipient Factors
Lung Allocation Score

http://optn.transplant.hrsa.gov/resources/professionalResources.asp?index=88
Lung Allocation Score (LAS)

Calculated using factors including age, disease type, disease severity, co-morbidities

Transplant Benefit Measure =

Post-transplant Survival Measure (est days survival in first year post transplant)
- Waitlist urgency (est days of survival without transplant)

Raw Allocation score =

Transplant Benefit Measure – Waitlist urgency

LAS: Normalization of RAS to 1-100

Intended use: “Likelihood of benefit from transplant” score—though weighted to favor those less likely to survive the coming year
Donor shortage

As of last week, 1700 patients are listed for lung transplants in the US.

In 2013, there were 2474 additions to the waitlist.

In 2013, there were only 1923 transplants from 8268 donors (only 23% of donors are lung donors).

UNOS lists 173 deaths on the list in 2012—does not include those removed when they became too ill to transplant.

Unsustainable: requires ever-increasing LAS to obtain offers.
“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
Donor Shortage

How to do better:

Obtain all appropriate donors
Donor management should maintain lungs
Optimize lung placement
Keep open mind regarding donor quality, donor types (DCD), and advancing intra-and ex-vivo lung resuscitative measures
Careful cooperative practice
Body Mass Index and 90-day Mortality

- Odds Ratio 3.7 for BMI < 17 kg/m² (p = 0.085)
- Odds Ratio 1.6 for BMI < 17 to 20 kg/m² (p = 0.455)
- Odds Ratio 3.5 for BMI > 25 to 27 kg/m² (p = 0.069)
- Odds Ratio 5.0 for BMI > 27 kg/m² (p = 0.003).

- Being overweight was associated with reduced mortality risk (hazard ratio (HR) 0.50, P = 0.042) compared to the normal BMI group

Ann Thorac Med. 2015 Jul-Sep;10(3):169-75
Performance status

- Increase in 6-minute walk is protective for operative risk

- All disease categories demonstrated significantly longer survival with increasing 6MWD ($P \leq 0.009$)

Castleberry AW et al. Am J Respir Crit Care Med. 2015 Oct 1;192(7):843-52
Lung Transplant

History and Survival

Indications-Referral -Workup

Transplant Coordination

Aftercare of Transplant Patients

On the Horizon
Successful Transplants Need a Team

- Surgeon
- Pulmonologist
- Nephrology
- Infectious Disease
- Home Healthcare Provider
- Intensivists
- Nutrition
- Palliative Care
- Endocrinology
- Respiratory Therapy
- PT/OT
- Cardiologist
- Nursing
- Pastoral
- Social Services
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?


Whitson BA et al. JHLT 2007 26:10:1004 -1011
Why Does PGD Matter?

Whitson BA et al. *JHLT* 2007 26:10:1004 -1011
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
Bronchiolitis Obliterans Syndrome – Denmark Group

Burton CM et al. JHLT 2007; 26: 681-6
Medical Issues after Transplantation

Acute Rejection
Chronic Rejection
Complications of Immunosuppression
Side effects of medications
Immunosuppression

Infection

Rejection
Three Drug 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

- 2000 (N = 589)
- 2003 (N = 825)
- July 2009 - June 2010 (N = 1,228)

% of Patients

Cyclosporine
Tacrolimus
Sirolimus
MMF
Azathioprine

ISHLT
2011
Acute Rejection

More common early after transplant
Usually “treatable”
Increases likelihood of chronic rejection
Treatment increases incidence of infection
Patients may demonstrate decreased graft function, non-specific symptoms or no symptoms
Chronic Rejection

Permanent loss of graft function over time
Can occur in as little as 3 months
May be difficult to diagnose
Prevalence: Varies with organ
Infections

Time-related risk:

0 - 4 months: Bacterial pathogens
2 wk – 1 year: CMV
Anytime: Fungal (including PCP)

Especially at risk:

Previous chronic disease
Pre-transplant immunosuppression
Augmentation of immunotherapy
Other infections
Hypogammaglobulinemia
  < 400 mg/dl IgG (Goldfarb, et al., 2001)
Prophylaxis: Fungus and PCP

Centers and different types of organs vary in prophylaxis practices.

Lungs are vulnerable because they are open to air.

Sulfa-based PCP prophylaxis has nearly eliminated PCP as a threat for transplant patients.

PCP prophylaxis is often lifelong.
Prophylaxis: Virus

CMV stays viable in tissues and blood
Previous exposure is very common in the adult population
(50-80%)
CMV can cause devastating short- and long-term complications
Especially vulnerable:
   Transplant recipients who have not yet been exposed to CMV who receive an organ from a donor who has been (CMV “Mismatch”)
Centers and different types of organs vary in prophylaxis practices

Encourage the influenza vaccine even though:
   Response decreased
   Protection not absolute
Avoid live virus vaccines such as MMR and polio
Novel Use of Medications:
It’s maybe not what you’d think

Azithromycin
Statins
Common Side Effects of Immunosuppressive Medications

Hypertension
Diabetes
Renal insufficiency
Neuromuscular dysfunction
Osteoporosis
Cataracts
Weight gain
Skin integrity
Gastrointestinal symptoms
Malaise
Relationship with Transplant Centers

Can be challenging
Encourage bilateral communication
Establish expectations
Ask for copies of protocols
If you have questions, ask
If you want to make changes, let them know
Lung Transplant

History and Survival
Indications - Referral - Workup
Transplant Coordination
Aftercare of Transplant Patients

On the Horizon
We Need To Expand the Donor Pool

- In 2013 there were 1923 lung transplants in the U.S.A.

- 23% conversion nationally

- In central Ohio, at Lifeline of Ohio, the local organ procurement organization, lung conversion rate was 18.8% in 2012
...Can We Keep A Lung Alive?

Expanding The Donor Pool

“Standard” Lung Donor Criteria

- Age less than 55 years
- ABO compatible
- Approximate size match
- Clear CXR
- $\text{PaO}_2/\text{FiO}_2$ more than 300 on 5 PEEP

- Tobacco history less than 20 pack-years
- Clear Bronchoscopy
- No primary pulmonary disease

Transplantable

Standard

Not Transplantable

Prohibitive
Expanding The Donor Pool

Ex-Vivo Lung Perfusion (EVLP)

Gas for deoxygenation
86% N₂, 8% CO₂, 6% O₂

Leukocyte filter

Membrane Deoxygenator

Pump

XVIVO Chamber with Lungs

ICU Ventilator

Courtesy XVIVO Perfusion
EVLP Technologies

Transmedics OCS (Organ Care System)

XVIVO Perfusion System (XPS)
What Does EVLP Allow Us to Do?

- Develop metrics to assess organ function
- Develop approaches to mitigate acute organ injury and recondition organs
- Modify or protect organs to enhance resistance to future injury
<table>
<thead>
<tr>
<th>Study</th>
<th>EVLP Tx N</th>
<th>As of 3/15/2014 = 58</th>
</tr>
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<tbody>
<tr>
<td>HELP</td>
<td>20</td>
<td></td>
</tr>
<tr>
<td>Expanded HELP</td>
<td>61+</td>
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<tr>
<td>NOVEL</td>
<td>31</td>
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## Clinical Trials

<table>
<thead>
<tr>
<th>HELP N=20</th>
<th>NOVEL N=31</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prospective, non-randomized, <strong>single-center</strong></td>
<td>Prospective, non-randomized, <strong>multi-center</strong></td>
</tr>
<tr>
<td>ISHLT Extended criteria Lungs</td>
<td>ISHLT Extended criteria Lungs</td>
</tr>
<tr>
<td>4 hours of EVLP using STEEN Solution™</td>
<td>4 hours of EVLP using STEEN Solution™</td>
</tr>
<tr>
<td>Using a $\Delta PaO_2 \geq 350$ at 2hr, 3hr, or 4 hr of ex vivo perfusion as transplantable with clinician approval of all variables</td>
<td>Using a $\Delta PaO_2 \geq 350$ at 2hr, 3hr, or 4hr <strong>(2 consecutive)</strong> of ex vivo perfusion as transplantable with clinician approval of all variables</td>
</tr>
<tr>
<td>Control group are conventional transplants at the same time period</td>
<td>Control group are conventional transplants at the same time period</td>
</tr>
<tr>
<td>Endpoints of 30 day survival, PGD, ICU and Hospital LOS</td>
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</tr>
</tbody>
</table>
HELP vs. NOVEL Trial

Courtesy XVIVO Perfusion
NOVEL Trial

- Prospective, non-randomized, multicenter, controlled clinical trial
  - University of Maryland Medical Center
  - Brigham and Women’s Hospital
  - NY Presbyterian-Columbia University Hospital
  - University of Colorado Medical Center
  - Duke University Medical Center
  - University of Pennsylvania Medical Center
NOVEL Trial Study Design

Donor Lungs Allocated per UNOS Standard Allocation Process (LAS Score and Donor/Recip Factors)

Rejected for Standard Transplant
Median PO₂ = 341

Lung Blocks Placed on EVLP N=54

Deemed Non-Transplantable
N=25

Deemed Transplantable
N=29

Recipients
N=31

Accepted for Standard Transplant
Median PO₂ = 421

Deemed Transplantable
N=31

Recipients
N=31*

Courtesy XVIVO Perfusion
Unacceptable Donor Definition

• Group A: \( \text{PaO}_2/\text{FiO}_2 \leq 300\text{mmHg} \)

  OR

• Group B: \( \text{PaO}_2/\text{FiO}_2 > 300\text{mmHg} \)
  – One or more factors makes them unacceptable for transplant
    • Multiple blood transfusions.
    • Pulmonary edema detected via CXR, bronchoscopy or palpation of lungs.
    • Donation after Circulatory Death (DCD).
    • Investigator evaluation of donor lung as “unsuitable” for standard criteria for lung transplant.
NOVEL Trial Overview

Pre-EVLP Assessment → EVLP with STEEN Solution™ → Post-EVLP

- 1hr
- 2hr
- 3hr
- 4hr

Physiological Parameters Assessed

- **XPS™ Hemodynamic Monitor**
  - PVR (Pulmonary Vascular Resistance)
  - PAP (Pulmonary Artery Pressure)
  - LAP (Left Arterial Pressure)
- **XPS™ Hamilton ICU Ventilator**
  - Peak awP (Peak Airway Pressure)
  - Mean awP (Mean Airway Pressure)
  - pPlat (peak Plateau)
  - cDyn (Dynamic compliance)
  - cStat (Static compliance)
  - $V_T$ (Tidal Volume)

- **Blood Gas Machine**
  - PaO2 (Pulmonary Artery Oxygen)
  - PvO2 (Pulmonary Vein Oxygen)

Transplanted → Not Transplanted

Courtesy XVIVO Perfusion
## NOVEL Trial Primary End Point

<table>
<thead>
<tr>
<th>Group</th>
<th>EVLP Transplant</th>
<th>Control Transplant</th>
<th>ISHLT Registry Reference*</th>
</tr>
</thead>
<tbody>
<tr>
<td>30 day patient survival</td>
<td>97% (30/31)</td>
<td>100% (31/31)</td>
<td>94%</td>
</tr>
<tr>
<td>90 day patient survival</td>
<td>97% (30/31)</td>
<td>100% (31/31)</td>
<td>88%</td>
</tr>
</tbody>
</table>

*Courtesy XVIVO Perfusion*
Novel Trial 12-Month Survival

NOVEL 12-Month Survival

Survival

Day

0% 20% 40% 60% 80% 100%

0 90 180 270 365

Control (N=31)
EVLP (N=31)
ISHLT

94%
88%
83%
p=0.35

Courtesy XVIVO Perfusion
## NOVEL Trial Donor Characteristics

<table>
<thead>
<tr>
<th>Donor Data</th>
<th>EVLP n=54*</th>
<th>Controls n=31</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median (range)</td>
<td>29 (13-65)</td>
<td>37 (19-62)</td>
<td>0.03</td>
</tr>
<tr>
<td>Mean (stdev)</td>
<td>31.2 ± 13.4</td>
<td>36.9 ± 13.1</td>
<td></td>
</tr>
<tr>
<td>M/F</td>
<td>29/25</td>
<td>21/10</td>
<td>0.26</td>
</tr>
<tr>
<td>BD/DCD</td>
<td>47/7</td>
<td>30/1</td>
<td>0.25</td>
</tr>
<tr>
<td>Cause of death</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CVA/stroke</td>
<td>11</td>
<td>10</td>
<td>0.30</td>
</tr>
<tr>
<td>Trauma</td>
<td>25</td>
<td>11</td>
<td>0.37</td>
</tr>
<tr>
<td>Hypoxia/anoxia</td>
<td>18</td>
<td>10</td>
<td>1.00</td>
</tr>
<tr>
<td>PaO₂ in donor</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median (range)</td>
<td>347 (119-501)</td>
<td>411 (285-589)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Mean (stdev)</td>
<td>335 ± 91</td>
<td>422 ± 79.2</td>
<td></td>
</tr>
<tr>
<td>CMV (+)</td>
<td>22</td>
<td>16</td>
<td>0.37</td>
</tr>
<tr>
<td>Smoking history</td>
<td>22</td>
<td>13</td>
<td>1.00</td>
</tr>
<tr>
<td>BAL (+)</td>
<td>21</td>
<td>15</td>
<td>1.00</td>
</tr>
</tbody>
</table>

* More lungs were tested than transplanted. This table shows all lungs placed on EVLP.
NOVEL Trial Outcome of EVLP Lungs

Lung Placed onto EVLP N=90

Bilateral N=72
- Discarded Prior to Tx N=36
  - 30 Lungs Tx into 15 Recipients as Bilaterals
- Accepted for Tx N=36
  - 5 Lungs Tx as Singles (1 lung rejected)

Single N=18
- Discarded Prior to Tx N=7
- Accepted for Tx N=11
  - 11 Lungs Tx into 11 Recipients as Singles

Courtesy XVIVO Perfusion
# NOVEL Trial Secondary End Points

<table>
<thead>
<tr>
<th>Lung Tx Outcomes</th>
<th>ISHLT Reference Data</th>
<th>EVLP Transplant N=31</th>
<th>Control N=31</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>72 hr PGD (adjusted)** Grade 3</td>
<td>18%</td>
<td>1** (3%)</td>
<td>1 (3%)</td>
<td>0.48</td>
</tr>
<tr>
<td>Patients ECLS post Tx # Days</td>
<td>n/a</td>
<td>2* (6%)</td>
<td>1 (3%)</td>
<td>1.0</td>
</tr>
<tr>
<td>Mech Ventilation Days Median (Range)</td>
<td>n/a</td>
<td>1 (1-196)</td>
<td>1 (1-29)</td>
<td>0.49</td>
</tr>
<tr>
<td>ICU Stay Days Median (Range)</td>
<td>n/a</td>
<td>4 (1-197)</td>
<td>3 (1-144)</td>
<td>0.68</td>
</tr>
<tr>
<td>Hospital Stay Days Median (Range)</td>
<td>n/a</td>
<td>13 (4-198)</td>
<td>11 (6-236)</td>
<td>0.13</td>
</tr>
</tbody>
</table>

*/*** Adjusted for 2 patients placed on extracorporeal membrane oxygenation (ECMO) prior to Tx in the OR.

Courtesy XVIVO Perfusion
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?


Whitson BA et al. *JHLT* 2007 26:10:1004-1011
Normothermic Ex Vivo Lung Perfusion in Clinical Lung Transplantation

Marcelo Cypel, M.D., Jonathan C. Yeung, M.D., Mingyao Liu, M.D., Masaki Anraku, M.D., Fengshi Chen, M.D., Ph.D., Wojtek Karolak, M.D., Masaaki Sato, M.D., Ph.D., Jane Laratta, R.N., Sassan Azad, C.R.A., Mindy Madonik, C.C.P., Chung-Wai Chow, M.D., Cecilia Chaparro, M.D., Michael Hutcheon, M.D., Lianne G. Singer, M.D., Arthur S. Slutsky, M.D., Kazuhiro Yasufuku, M.D., Ph.D., Marc de Perrot, M.D., Andrew F. Pierre, M.D., Thomas K. Waddell, M.D., Ph.D., and Shaf Keshavjee, M.D.
Expanding The Donor Pool

Expanding The Donor Pool

### Expanding The Donor Pool

<table>
<thead>
<tr>
<th>End Point</th>
<th>Donors without a Heartbeat (N = 9)</th>
<th>Brain-Dead Donors (N = 11)</th>
<th>Total (N = 20)</th>
<th>Absolute Difference† (percentage points (95% CI))</th>
<th>P Value‡</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary end point§</strong></td>
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<tr>
<td>PGD grade 2 or 3 at 72 hr (%)</td>
<td>11</td>
<td>18</td>
<td>15</td>
<td>30</td>
<td>0.11</td>
</tr>
<tr>
<td><strong>Secondary end points§</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PGD grade 2 or 3 at ICU arrival (%)</td>
<td>33</td>
<td>18</td>
<td>25</td>
<td>30</td>
<td>0.30</td>
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<tr>
<td>PGD grade 2 or 3 at 24 hr (%)</td>
<td>11</td>
<td>18</td>
<td>15</td>
<td>36</td>
<td>0.07</td>
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<tr>
<td>PGD grade 2 or 3 at 48 hr (%)</td>
<td>33</td>
<td>27</td>
<td>30</td>
<td>35</td>
<td>0.46</td>
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<tr>
<td>ECMO (%)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>4</td>
<td>0.37</td>
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<tr>
<td>PaO₂/FiO₃ on arrival in ICU (mm Hg)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.51</td>
</tr>
<tr>
<td>Median</td>
<td>420</td>
<td>423</td>
<td>422</td>
<td>372</td>
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<tr>
<td>Range</td>
<td>85–518</td>
<td>86–538</td>
<td>85–538</td>
<td>49–591</td>
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<tr>
<td>Mechanical ventilation after transplantation (days)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.15</td>
</tr>
<tr>
<td>Median</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Range</td>
<td>1–27</td>
<td>1–101</td>
<td>1–101</td>
<td>1–43</td>
<td></td>
</tr>
<tr>
<td>ICU stay after transplantation (days)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.68</td>
</tr>
<tr>
<td>Median</td>
<td>4</td>
<td>5</td>
<td>4</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Range</td>
<td>1–34</td>
<td>1–101</td>
<td>1–101</td>
<td>1–103</td>
<td></td>
</tr>
<tr>
<td>Hospital stay after transplantation (days)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.39</td>
</tr>
<tr>
<td>Median</td>
<td>19</td>
<td>34</td>
<td>23</td>
<td>27</td>
<td></td>
</tr>
<tr>
<td>Range</td>
<td>7–54</td>
<td>11–101</td>
<td>7–101</td>
<td>9–156</td>
<td></td>
</tr>
<tr>
<td>Airway complications (%)¶</td>
<td>11</td>
<td>0</td>
<td>5</td>
<td>4</td>
<td>1.0</td>
</tr>
<tr>
<td>Mortality at 30 days (%)</td>
<td>22</td>
<td>0</td>
<td>10</td>
<td>5</td>
<td>0.33</td>
</tr>
</tbody>
</table>
What Does EVLP Allow Us to Do?

Successful emergent lung transplantation after remote ex vivo perfusion optimization and transportation of donor lungs.


Wigfield CH et al., Am J Transplant 2012 12(10):2838-44
Experience with the first 50 ex vivo lung perfusions in clinical transplantation

Marcelo Cypel, MD, MSc, Jonathan C. Yeung, MD, PhD, Tiago Machuca, MD, Manyin Chen, MD, Lianne G. Singer, MD, Kazuhiro Yasufuku, MD, PhD, Marc de Perrot, MD, MSc, Andrew Pierre, MD, MSc, Thomas K. Waddell, MD, PhD, and Shaf Keshavjee, MD, MSc
<table>
<thead>
<tr>
<th>Donor variable</th>
<th>EVLP (n = 50)</th>
<th>Controls (n = 253)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>45</td>
<td>45</td>
<td>.52</td>
</tr>
<tr>
<td>DCD (%)</td>
<td>44</td>
<td>5.1</td>
<td>.0001</td>
</tr>
<tr>
<td>Best P/F ratio (mm Hg)</td>
<td>334</td>
<td>452</td>
<td>.0001</td>
</tr>
<tr>
<td>Chest x-ray abnormalities (%)</td>
<td>67</td>
<td>45</td>
<td>.001</td>
</tr>
<tr>
<td>Positive BAL cultures (%)</td>
<td>70</td>
<td>55</td>
<td>.05</td>
</tr>
<tr>
<td>Recipient variable</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>56</td>
<td>56</td>
<td>.68</td>
</tr>
<tr>
<td>Diagnosis of pulmonary fibrosis or PAH (%)</td>
<td>32</td>
<td>38.7</td>
<td>.42</td>
</tr>
<tr>
<td>Transplantation variable</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Bilateral (%)</td>
<td>76</td>
<td>88</td>
<td>.04</td>
</tr>
<tr>
<td>Retransplantation (%)</td>
<td>2</td>
<td>3.5</td>
<td>1.00</td>
</tr>
<tr>
<td>Cardiopulmonary bypass (%)</td>
<td>30</td>
<td>39</td>
<td>.26</td>
</tr>
</tbody>
</table>
Cypel M et al., JTCVS 2012 144(5):1200-7
The First 50 Clinical EVLP: Toronto Experience

Cypel M et al., JTCVS 2012 144(5):1200-7
EVLP: French Experience

- 31 EVLP Lungs
- 81 Standard

Sage E et al., EJCTS 2014 1-6
Resolution of PGD

- Italian Study
- 8 EVLP
- 28 Standard
- PGD @ 0 hrs and 72 hrs

<table>
<thead>
<tr>
<th></th>
<th>Overall (n = 36)</th>
<th>Group A (n = 28)</th>
<th>Group B (n = 8)</th>
<th>P</th>
<th>Overall (n = 36)</th>
<th>Group A (n = 28)</th>
<th>Group B (n = 8)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>PGD 0-1</td>
<td>36 ± 4.1% (13)</td>
<td>29 ± 10.5% (8)</td>
<td>63 ± 43.3% (5)</td>
<td>0.11</td>
<td>62 ± 20.1% (22)</td>
<td>54 ± 19.8% (15)</td>
<td>88 ± 60.6% (7)</td>
<td>0.10</td>
</tr>
<tr>
<td>PGD 2</td>
<td>17 ± 5.4% (6)</td>
<td>21 ± 7.6% (6)</td>
<td>0% (0)</td>
<td>0.19</td>
<td>19 ± 6.0% (7)</td>
<td>21 ± 7.6% (6)</td>
<td>12 ± 7.9% (1)</td>
<td>0.65</td>
</tr>
<tr>
<td>PGD 3</td>
<td>47 ± 15.2% (17)</td>
<td>50 ± 18.3% (14)</td>
<td>37 ± 25.3% (3)</td>
<td>0.57</td>
<td>19 ± 6.0% (7)</td>
<td>25 ± 9.1% (7)</td>
<td>0% (0)</td>
<td>0.14</td>
</tr>
</tbody>
</table>

Boffini ME et al., EJCTS 2014 1-5
Delayed EVLP: Porcine Model - UVA

Mulloy DP et al., JTCVS 2012 144(5):1208-16
EVLP Could Increase Lung Utilization

- HELP trial = 20 EVLP lung transplants. Lung utilization rate increased from 25% to 36%
- NOVEL trial = 54 initially unacceptable donor lungs placed on EVLP
  - 29 lung donors meeting acceptability for transplant into 31 recipients
EVLP is Safe

<table>
<thead>
<tr>
<th>Lung Tx Outcomes</th>
<th>ISHLT* Reference Data</th>
<th>SRTR** Reference Data</th>
<th>NOVEL EVLP Transplant</th>
</tr>
</thead>
<tbody>
<tr>
<td>30 day survival</td>
<td>94%</td>
<td>96%</td>
<td>97%</td>
</tr>
<tr>
<td>1 year survival</td>
<td>81%</td>
<td>82%</td>
<td>84%</td>
</tr>
</tbody>
</table>

* ISHLT: International Society of Heart and Lung Transplant Registry.
** SRTR: Scientific Registry of Transplant Recipients.
Summary

Lung transplant outcomes have improved over the past two decades

Lung Transplantation is an option for some patients with advanced-stage lung disease

Post-transplant management can be challenging but knowledge, experience, and good communication help

Ex-vivo organ perfusion may expand the potential donor pool and allow for donor organ functional improvement.
Acknowledgements

- Drs. Pope-Harman, Kirkby, Shah & Hayes
- Drs. Crestanello, Rushing, Black, Kilic and Lee
- Lifeline of Ohio

- XVIVO Perfusion
- Drs. Keshavjee and Cypel and the University of Toronto
- OSUWMC Lung Transplant Team, Ross Perfusionists & OR Staff
- Drs. Papadimos, Tripathi, Flores, Essandoh & Andritsos
- Many many others…
Remember…

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Fax: 164-293-9820