Referral for Lung Transplantation for Patients with Pulmonary Hypertension (Lung Transplant and Extracorporeal Support)

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Objectives

- Today we will review
  1. Epidemiology of lung transplant
  2. Indications and contraindications for lung transplant
  3. Timing of referral and listing for lung transplantation in patients with pulmonary arterial hypertension
  4. Post transplant management and complications
  5. ECMO for lung transplantation
History
Lung Transplant

- **Historical Background**
  - 1963 Dr. James Hardy performs the first human lung transplant in Jackson, MS on a prisoner with COPD and lung cancer. Survived 18 days post transplant
  - 1981 Dr. Bruce Reitz performs the first successful heart-lung transplant for PAH at Stanford
  - 1983 Cyclosporine is released as a novel immunosuppression medication
  - 1983 first successful single lung transplantation by Dr. Joel Cooper with the Toronto Lung Transplant Group in a 58 year old with IPF
  - 1986 En-bloc double lung transplant is performed by Dr. Joel Cooper with the Toronto Lung Transplant Group
  - 1989 Bilateral sequential lung transplant is performed by Dr. Michael Pasque and Dr. Joel Cooper at Washington University in St. Louis
Epidemiology
Adult Lung Transplants
Indications (Transplants: Jan 1995-June 2016)

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>SLT (N=18,207)</th>
<th>BLT (N=36,046)</th>
<th>TOTAL (N=54,253)</th>
</tr>
</thead>
<tbody>
<tr>
<td>COPD</td>
<td>7,266 (39.9%)</td>
<td>9,539 (26.5%)</td>
<td>16,805 (31.0%)</td>
</tr>
<tr>
<td>IIP</td>
<td>6,449 (35.4%)</td>
<td>6,990 (19.4%)</td>
<td>13,439 (24.8%)</td>
</tr>
<tr>
<td>CF</td>
<td>218 (1.2%)</td>
<td>8,266 (22.9%)</td>
<td>8,484 (15.6%)</td>
</tr>
<tr>
<td>ILD-not IIP</td>
<td>1,078 (5.9%)</td>
<td>1,925 (5.3%)</td>
<td>3,003 (5.5%)</td>
</tr>
<tr>
<td>A1ATD</td>
<td>797 (4.4%)</td>
<td>1,912 (5.3%)</td>
<td>2,709 (5.0%)</td>
</tr>
<tr>
<td>Retransplant</td>
<td>922 (5.1%)</td>
<td>1,269 (3.5%)</td>
<td>2,191 (4.0%)</td>
</tr>
<tr>
<td>IPAH</td>
<td>88 (0.5%)</td>
<td>1,481 (4.1%)</td>
<td>1,569 (2.9%)</td>
</tr>
<tr>
<td>Non CF-bronchiectasis</td>
<td>67 (0.4%)</td>
<td>1,413 (3.9%)</td>
<td>1,480 (2.7%)</td>
</tr>
<tr>
<td>Sarcoidosis</td>
<td>312 (1.7%)</td>
<td>1,026 (2.8%)</td>
<td>1,338 (2.5%)</td>
</tr>
<tr>
<td>PH-not IPAH</td>
<td>135 (0.7%)</td>
<td>690 (1.9%)</td>
<td>825 (1.5%)</td>
</tr>
<tr>
<td>LAM/tuberous sclerosis</td>
<td>146 (0.8%)</td>
<td>381 (1.1%)</td>
<td>527 (1.0%)</td>
</tr>
<tr>
<td>OB</td>
<td>73 (0.4%)</td>
<td>395 (1.1%)</td>
<td>468 (0.9%)</td>
</tr>
<tr>
<td>CTD</td>
<td>140 (0.8%)</td>
<td>282 (0.8%)</td>
<td>422 (0.8%)</td>
</tr>
<tr>
<td>Cancer</td>
<td>7 (0.0%)</td>
<td>27 (0.1%)</td>
<td>34 (0.1%)</td>
</tr>
<tr>
<td>Other</td>
<td>509 (2.8%)</td>
<td>450 (1.2%)</td>
<td>959 (1.8%)</td>
</tr>
</tbody>
</table>
Adult Lung Transplants
Major Indications by Year (Number)

Transplant Year

Number of Transplants

0 500 1,000 1,500 2,000 2,500 3,000 3,500 4,000

COPD  A1ATD  CF  IIP  ILD-not IIP  Retransplant

2017 JHLT. 2017 Oct; 36(10): 1037-1079
Adult Lung Transplants
Kaplan-Meier Survival by Era
(Transplants: Jan 1990-June 2015)
Adult Lung Transplants
Kaplan-Meier Survival by Diagnosis
(Transplants: Jan 1990-June 2015)

Median survival (years):
A1ATD: 6.7; CF: 9.2; COPD: 5.8; IIP: 4.9;
ILD-not IIP: 6.0; Retransplant: 2.9
Adult Lung Transplants
Kaplan-Meier Survival by Diagnosis
(Transplants: January 1990 – June 2012)

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
#### Cause of Death
(Deaths: Jan 1990-June 2016)

<table>
<thead>
<tr>
<th>Cause of Death</th>
<th>0-30 Days (N=3,574)</th>
<th>31 Days - 1 Year (N=6,367)</th>
<th>&gt;1 Year - 3 Years (N=6,194)</th>
<th>&gt;3 Years - 5 Years (N=3,656)</th>
<th>&gt;5 Years - 10 Years (N=4,578)</th>
<th>&gt;10 Years (N=1,837)</th>
</tr>
</thead>
<tbody>
<tr>
<td>OB/BOS</td>
<td>10 (0.3%)</td>
<td>292 (4.6%)</td>
<td>1,633 (26.4%)</td>
<td>1,095 (30.0%)</td>
<td>1,146 (25.0%)</td>
<td>407 (22.2%)</td>
</tr>
<tr>
<td>Acute Rejection</td>
<td>115 (3.2%)</td>
<td>114 (1.8%)</td>
<td>92 (1.5%)</td>
<td>20 (0.5%)</td>
<td>21 (0.5%)</td>
<td>4 (0.2%)</td>
</tr>
<tr>
<td>Lymphoma</td>
<td>1 (0.0%)</td>
<td>137 (2.2%)</td>
<td>107 (1.7%)</td>
<td>54 (1.5%)</td>
<td>83 (1.8%)</td>
<td>56 (3.0%)</td>
</tr>
<tr>
<td>Malignancy, Non-Lymphoma</td>
<td>5 (0.1%)</td>
<td>193 (3.0%)</td>
<td>514 (8.3%)</td>
<td>430 (11.8%)</td>
<td>676 (14.8%)</td>
<td>258 (14.0%)</td>
</tr>
<tr>
<td>CMV</td>
<td>3 (0.1%)</td>
<td>129 (2.0%)</td>
<td>55 (0.9%)</td>
<td>9 (0.2%)</td>
<td>6 (0.1%)</td>
<td>1 (0.1%)</td>
</tr>
<tr>
<td>Infection, Non-CMV</td>
<td>682 (19.1%)</td>
<td>2,213 (34.8%)</td>
<td>1,290 (20.8%)</td>
<td>655 (17.9%)</td>
<td>785 (17.1%)</td>
<td>303 (16.5%)</td>
</tr>
<tr>
<td>Graft Failure</td>
<td>870 (24.3%)</td>
<td>1,039 (16.3%)</td>
<td>1,162 (18.8%)</td>
<td>651 (17.8%)</td>
<td>737 (16.1%)</td>
<td>277 (15.1%)</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>429 (12.0%)</td>
<td>345 (5.4%)</td>
<td>275 (4.4%)</td>
<td>173 (4.7%)</td>
<td>267 (5.8%)</td>
<td>120 (6.5%)</td>
</tr>
<tr>
<td>Technical</td>
<td>414 (11.6%)</td>
<td>226 (3.5%)</td>
<td>55 (0.9%)</td>
<td>17 (0.5%)</td>
<td>33 (0.7%)</td>
<td>13 (0.7%)</td>
</tr>
<tr>
<td>Multiple Organ Failure</td>
<td>440 (12.3%)</td>
<td>766 (12.0%)</td>
<td>319 (5.2%)</td>
<td>151 (4.1%)</td>
<td>213 (4.7%)</td>
<td>98 (5.3%)</td>
</tr>
<tr>
<td>Other</td>
<td>605 (16.9%)</td>
<td>913 (14.3%)</td>
<td>692 (11.2%)</td>
<td>401 (11.0%)</td>
<td>611 (13.3%)</td>
<td>300 (16.3%)</td>
</tr>
</tbody>
</table>
Referral, Listing, Special Considerations
Lung transplantation is indicated for patients with end stage lung disease for which maximal medical therapy is ineffective or there is no proven therapy.
General indication

- Should be considered for adults with chronic, end-stage lung disease who meet all the following general criteria:
  - High (>50%) risk of death from lung disease within 2 years if lung transplantation is not performed
  - High (>80%) likelihood of surviving at least 90 days after lung transplantation
  - High (>80%) likelihood of 5-year post-transplant survival from a general medical perspective provided that there is adequate graft function

- Disease specific indications exist and those for PAH will be discussed later
Absolute Contraindications

- Malignancy within the last 2 years with the exception of non-melanoma skin cancers
  - 5 year disease free interval is necessary for most cancers
    - Extracapsular renal cell tumors
    - Breast cancer that is stage 2 or higher
    - Colon cancer staged higher than Dukes A
    - Melanoma, level III or higher

- Untreatable significant dysfunction of another organ system unless a combined organ transplant can be preformed

- Uncorrected atherosclerotic disease with suspected or confirmed end organ ischemia or coronary artery disease not amenable to revascularization
Absolute Contraindications

- Acute medical instability
- Uncorrectable bleeding diathesis
- Chronic *infections* with highly virulent and/or resistant microbes
- Significant chest wall or spinal deformities
- Class II or III obesity (BMI >35.0 kg/m2)
- Medical non-adherence
- Psychiatric or psychologic conditions associated with inability to cooperate with the medical team or adhere to complex medical therapy
- Poor or unreliable social support system
- Severely limited functional status with poor rehabilitation potential
- Substance abuse
Relative Contraindications

- Age >65 years in association with low physiologic reserve and/or other relative contraindications
- Class I obesity (BMI 30.0-34.9 kg/m²)
- Severe malnutrition
- Severe osteoporosis
- Prior chest surgeries or lung resection
- Mechanical ventilation and/or extracorporeal life support
- Patients infected with hepatitis B and/or C
- Patients with HIV
Relative Contraindications

- Patients with coronary artery disease
  - May undergo percutaneous intervention before transplantation or coronary artery bypass grafting

- *Colonization* with highly resistant or highly virulent bacteria, fungi, and certain strains of mycobacteria

- Other medical conditions that have not resulted in end-stage organ damage, such as diabetes mellitus, systemic hypertension, epilepsy, central venous obstruction, peptic ulcer disease, or gastroesophageal reflux
  - Should be optimally treated before transplant
Referral for Lung Transplant Evaluation

- Generally, patients should be referred when:
  - 2-3 year survival is expected to be less than 50%
  - NYHA Functional Class is III-IV

- Early referral is preferred for patients with higher waiting list mortality (IPF, PH, CF)
Predicting Mortality for IPAH

- U.S. Registry to Evaluate Early and Long-term PAH Disease Management (REVEAL) identifies the following as factors for increased mortality:
  - NYHA Functional Class IV
  - Male gender with age >60 years old
  - Increased pulmonary vascular resistance
  - PAH associated with portal hypertension
  - Family history of PAH

- Currently no equations to predict waiting list mortality in patients with IPAH
Disease Specific Indication
Pulmonary Vascular Disease

- Timing of referral
  - NYHA Functional Class III or IV symptoms on escalating therapy
  - Rapidly progressive disease
  - Use of parenteral targeted PAH therapy regardless of symptoms or NYHA Functional Class
  - Known or suspected pulmonary veno-occlusive disease or pulmonary capillary hemangiomatosis

- Targeted medical therapy has led to a marked change in the timing for referral and listing for patients with IPAH
Timing of transplant listing

- NYHA Functional Class III or IV despite a trial of at least 3 months of combination therapy including prostanoids
- Cardiac index of <2 L/min/m2
- Mean right atrial pressure of >15mm Hg
- 6 minute walk test of <350 m
- Development of significant hemoptysis, pericardial effusion, or signs of progressive right heart failure
In May 2005, UNOS adopted the LAS which prioritized waiting list candidates based on a combination of waitlist urgency and post transplant survival.

**Goals**
- Reduce number of deaths on the lung transplant list
- Increase transplant benefit for lung recipients
- Ensure the efficient and equitable allocation of lungs to active transplant candidates

With the previous system, lungs were allocated based on time on the wait list.
Lung Allocation Score

- Waitlist urgency measure
  - Expected number of days lived without a transplant during an additional year on the waitlist

- Post-transplant survival measure
  - Expected number of days lived during the first year post transplant
Lung Allocation Score

- Favors: IPF > CF > COPD > PH
- Diagnosis by group:

**Table 3: Diagnosis groups and their constituent diagnoses**

<table>
<thead>
<tr>
<th>Group A</th>
<th>Group B</th>
<th>Group C</th>
<th>Group D</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronic obstructive pulmonary disease (COPD)</td>
<td>Primary pulmonary hypertension (PPH)</td>
<td>Cystic fibrosis (CF)</td>
<td>Idiopathic pulmonary fibrosis (IPF)</td>
</tr>
<tr>
<td>Emphysema</td>
<td>Eisenmenger’s syndrome</td>
<td>Immune deficiency syndromes, e.g. IgG deficiency</td>
<td>All other restrictive lung diseases, including hemosiderosis</td>
</tr>
<tr>
<td>Alpha-one antitrypsin deficiency</td>
<td>All specific pulmonary vascular diseases, including pulmonary venous obstructive disease, chronic pulmonary thromboembolic disease</td>
<td></td>
<td>Eosinophilic granulomatosis</td>
</tr>
<tr>
<td>emphysema</td>
<td></td>
<td></td>
<td>Sarcoïdosis with mean PA pressure &gt;30 mmHg</td>
</tr>
<tr>
<td>Bronchiectasis, including primary ciliary dyskinesia</td>
<td></td>
<td></td>
<td>Scleroderma/CREST</td>
</tr>
<tr>
<td>Lymphangioleiomyomatosis (LAM)</td>
<td></td>
<td></td>
<td>Bronchoalveolar carcinoma (BAC)</td>
</tr>
<tr>
<td>Sarcoidosis with mean PA pressure ≤ 30 mmHg</td>
<td></td>
<td></td>
<td>Bronchiolitis obliterans syndrome (BOS) following lung transplant</td>
</tr>
</tbody>
</table>

Source: SRTR.
**Table 5:** Factors used to calculate LAS when the allocation system was implemented

<table>
<thead>
<tr>
<th>Factors used to predict waiting list survival</th>
<th>Factors used to predict posttransplant survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>FVC (% predicted)</td>
<td>FVC (% predicted)</td>
</tr>
<tr>
<td>PA systolic pressure</td>
<td>PCW mean pressure $\geq$ 20 mmHg</td>
</tr>
<tr>
<td>$O_2$ required at rest (L/min)</td>
<td>Continuous mechanical ventilation</td>
</tr>
<tr>
<td>Age at offer</td>
<td>Age at transplant</td>
</tr>
<tr>
<td>Body mass index (BMI)</td>
<td>Serum creatinine (mg/dL)</td>
</tr>
<tr>
<td>NYHA functional status</td>
<td>NYHA functional status</td>
</tr>
<tr>
<td>Diagnosis</td>
<td>Diagnosis</td>
</tr>
<tr>
<td>Six-minute walk distance &lt;150 feet</td>
<td></td>
</tr>
<tr>
<td>Continuous mechanical ventilation</td>
<td></td>
</tr>
<tr>
<td>Diabetes</td>
<td></td>
</tr>
</tbody>
</table>

Source: SRTR.
Lung Allocation Score

Date of birth: 04/24/1960
Height: 5 ft 5 in (165.1 cm)
Weight: 150 lbs (68.039 kg)
Lung diagnosis code: IDIOPATHIC PULMONARY FIBROSIS (IPF)
Functional status: Performs activities of daily living with SOME assistance.
Diabetes: Insulin dependent
Assisted ventilation: No assisted ventilation needed
Requires supplemental O₂:
  - Amount: 3 L/min
  - %
Percent predicted FVC:
  - 35%
Six minute walk distance:
  - 800 feet
Pulmonary artery systolic pressure:
  - 80 mmHg
Mean pulmonary artery pressure:
  - 50 mmHg
Cardiac index (CI):
  - 2 L/min/m²
Central venous pressure (CVP):
  - 12 mmHg

Serum creatinine:
  - Current: 1.2 mg/dL
  - Highest: 1.8 mg/dL
  - Lowest: 1 mg/dL
Total bilirubin:
  - Current: 1.5 mg/dL
  - Highest: 2 mg/dL
  - Lowest: 1 mg/dL

Note: If using a central venous test
  6 mmHg before entering the

Lung allocation score (LAS): 77.4048
Waitlist urgency measure: 303 day(s)
Post-transplant survival measure: 323 day(s)
Lung Allocation Score

Date of birth: 04/24/1960
Height: 5 ft 5 in
5 ft 5 in = 165.1 cm
Weight: 150 lbs
150 lbs = 68.039 kg
Lung diagnosis code: PULMONARY HYPERTENSION/PULMONARY ARTERY
Functional status: Performs activities of daily living with SOME assistance.
Diabetes: Insulin dependent
Assisted ventilation: No assisted ventilation needed
Requires supplemental O₂:
Amount: 3 L/min
Percent predicted FVC:
80 %
Six minute walk distance:
800 feet
Pulmonary artery systolic pressure:
80 mmHg
Mean pulmonary artery pressure:
50 mmHg
Cardiac index (CI):
2 L/min/m²
Central venous pressure (CVP):
12 mmHg
PCO₂:
Current: 50 mmHg
Highest: 50 mmHg
Lowest: 50 mmHg

Note: If using a central venous test vs 6 mmHg before entering the va

Serum creatinine:
Current: 1.2 mg/dL
Highest: 1.8 mg/dL
Lowest: 1.5 mg/dL
Total bilirubin:
Current: 1.5 mg/dL
Highest: 2 mg/dL
Lowest: 1 mg/dL

Waitlist urgency measure
242 day(s)
Post-transplant survival measure
329 day(s)
Lung Allocation Score

- Exceptions for pulmonary hypertension (primary or secondary) patients can be made by making a formal request to UNOS for an LAS exception if they meet the following criteria:
  - Patient is deteriorating on optimal therapy, and
  - Patient has a right atrial pressure greater than 15 mm Hg or a cardiac index less than 1.8 L/min/m2

- If the exception is approved, then the patient will receive an LAS score corresponding to the 90th percentile
Lung vs Heart-Lung Transplant for PH

Interactive CardioVascular and Thoracic Surgery 17 (2013) 166–170

Should we perform bilateral-lung or heart-lung transplantation for patients with pulmonary hypertension?

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Type of Surgery

- No survival benefit between bilateral lung vs combined heart lung transplantation for pulmonary hypertension

- Heart-lung transplant shows better survival for
  - Congenital heart disease
  - Eisenmenger’s syndrome
  - RVEF <10%
  - LVEF <35%

- Gold standard now bilateral lung transplantation
Complications Post-Transplant Day 0-1 Month
Complications Specific to PH

- **Induction**
  - Can lead to RV failure and cardiac arrest

- **Intra-operative**
  - Acute RV failure (especially when not done on cardiopulmonary bypass)

- **Post-operative**
  - Acute RV failure
  - Acute LV failure
Primary Graft Dysfunction

- Form of ischemia-reperfusion injury
  - Reactive oxygen species generated during reperfusion from cold ischemia cause direct injury to pulmonary endothelium and epithelium

- Results in impaired oxygenation and decreased lung compliance

- Affects up to 25% of all lung transplant procedures and has no proven preventative therapy

- PGD increases 30-day mortality by eightfold

- PGD significantly increases the risk of bronchiolitis obliterans syndrome (BOS)
### Primary Graft Dysfunction

#### Table 4: Suggested PGD risk factors

<table>
<thead>
<tr>
<th>Category</th>
<th>Risk Factor for PGD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Donor variables (inherent):</td>
<td></td>
</tr>
<tr>
<td>Age &gt;45 y</td>
<td></td>
</tr>
<tr>
<td>African American race</td>
<td></td>
</tr>
<tr>
<td>Female gender</td>
<td></td>
</tr>
<tr>
<td>History of smoking &gt;10 pack years</td>
<td></td>
</tr>
<tr>
<td>Donor variables (acquired):</td>
<td></td>
</tr>
<tr>
<td>Prolonged mechanical ventilation</td>
<td></td>
</tr>
<tr>
<td>Aspiration</td>
<td></td>
</tr>
<tr>
<td>Head trauma</td>
<td></td>
</tr>
<tr>
<td>Hemodynamic instability post brain death</td>
<td></td>
</tr>
<tr>
<td>Recipient variables:</td>
<td></td>
</tr>
<tr>
<td>Body mass index &gt;25</td>
<td></td>
</tr>
<tr>
<td>Female gender</td>
<td></td>
</tr>
<tr>
<td>Diagnosis of idiopathic pulmonary arterial hypertension</td>
<td></td>
</tr>
<tr>
<td>Diagnosis of secondary pulmonary arterial hypertension</td>
<td></td>
</tr>
<tr>
<td>Elevated pulmonary arterial pressure at time of surgery</td>
<td></td>
</tr>
<tr>
<td>Diagnosis of diffuse parenchymal lung disease: pulmonary fibrosis</td>
<td></td>
</tr>
<tr>
<td>Operative variables:</td>
<td></td>
</tr>
<tr>
<td>Use of Eurocollins preservation solution</td>
<td></td>
</tr>
<tr>
<td>Single lung transplant</td>
<td></td>
</tr>
<tr>
<td>Prolonged ischemic time</td>
<td></td>
</tr>
<tr>
<td>Use of cardiopulmonary bypass</td>
<td></td>
</tr>
<tr>
<td>Blood product transfusion</td>
<td></td>
</tr>
</tbody>
</table>

- Bold indicates risk factors most consistently reported in the literature.
- Underlining indicates risk factors identified in Kuntz et al.83
Primary Graft Dysfunction

- Occurs within the first 72 hours post transplant

- Manifests as hypoxia and CXR findings consistent with pulmonary edema

- Must exclude other potential causes
  - Pulmonary vein thrombosis
  - Hyperacute rejection
  - Pneumonia
Primary Graft Dysfunction

- Diagnostic criteria developed by the ISHLT
- Evaluated at 0, 6, 24, 48, and 72 hours post transplant

### Table 1
ISHLT PGD grading schema

<table>
<thead>
<tr>
<th>Grade</th>
<th>$\text{Pao}_2$/Fio$_2$</th>
<th>Radiographic Infiltrates Consistent with Pulmonary Edema</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>$&gt;$300</td>
<td>Absent</td>
</tr>
<tr>
<td>1</td>
<td>$&gt;$300</td>
<td>Present</td>
</tr>
<tr>
<td>2</td>
<td>200–300</td>
<td>Present</td>
</tr>
<tr>
<td>3</td>
<td>$&lt;$200</td>
<td>Present</td>
</tr>
</tbody>
</table>

![Graph showing 30-Day Mortality (%) across different time points (T24, T48, T72) for different grades of PGD]
Primary Graft Dysfunction

- Prevention
  - No proven preventive measures
    - Use of Perfadex as a preservation solution showed a trend toward better oxygenation, ICU stay, and 30-day mortality

- Management remains supportive
  - Lung protective ventilation
  - Avoid fluid overload
  - Inhaled NO improves capillary integrity and prevents leukocyte and platelet aggregation
  - ECMO
Complications Post-Transplant 1 Month to 1 Year
Acute Rejection

- Acute Cellular Rejection
  - Driven by T-cell recognition of foreign MHC
  - Recruitment and activation of recipient lymphocytes to the graft leads to injury which in turn can lead to loss of function
  - Risk factors include suboptimal immunosuppression, GERD/chronic aspiration, and infections
  - Symptoms can vary and can include dyspnea, cough, hypoxia, chest pains, fever, fatigue, or no symptoms at all
Acute Rejection

- Diagnosis
  - Spirometry—not very specific
  - Radiography—low sensitivity
  - Gold standard is bronchoscopy with trans-bronchial biopsies

COMPLICATIONS OF BRONCHOSCOPY WITH TBBX IN LTx PATIENTS²

<table>
<thead>
<tr>
<th>Condition</th>
<th>Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Desaturation</td>
<td>11%</td>
</tr>
<tr>
<td>Pneumothorax</td>
<td>&lt;3%</td>
</tr>
<tr>
<td>Arrhythmia</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>&gt;100ml Bleed</td>
<td>4%</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>2%</td>
</tr>
<tr>
<td>MV</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>Mean 7±10ml loss</td>
<td></td>
</tr>
</tbody>
</table>

Similar to non-LTx
# Acute Rejection

<table>
<thead>
<tr>
<th>Category</th>
<th>Grade</th>
<th>Meaning</th>
<th>Appearance</th>
</tr>
</thead>
<tbody>
<tr>
<td>A: acute rejection</td>
<td>0</td>
<td>None</td>
<td>Normal lung parenchyma</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>Minimal</td>
<td>Inconspicuous small mononuclear perivascular infiltrates</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>Mild</td>
<td>More frequent, more obvious, perivascular infiltrates, eosinophils may be present</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>Moderate</td>
<td>Dense perivascular infiltrates, extension into interstitial space, can involve endothelialitis, eosinophils, and neutrophils</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>Severe</td>
<td>Diffuse perivascular, interstitial, and air-space infiltrates with lung injury. Neutrophils may be present.</td>
</tr>
<tr>
<td>B: airway inflammation</td>
<td>0</td>
<td>None</td>
<td>No evidence of bronchiolar inflammation</td>
</tr>
<tr>
<td></td>
<td>1R</td>
<td>Low grade</td>
<td>Infrequent, scattered or single layer mononuclear cells in bronchiolar submucosa</td>
</tr>
<tr>
<td></td>
<td>2R</td>
<td>High grade</td>
<td>Larger infiltrates of larger and activated lymphocytes in bronchiolar submucosa. Can involve eosinophils and plasmacytoid cells.</td>
</tr>
</tbody>
</table>
Acute Rejection

- Prevention: adequate immunosuppressive therapy
  - Calcineurin inhibitors (Tacrolimus, Cyclosporine): most important of all immunosuppressing agents for lung transplantation
    - Decreases IL-2 production and IL-2 mediated T-cell proliferation
    - Toxicities include renal failure, headaches, seizures, tremors, and PRES
  - Purine synthesis inhibitors (Mycophenolate, Azathioprine)
    - Inhibit de-novo synthesis of guanine nucleotides and which decreases production of both T and B cells
    - Toxicities include diarrhea and leukopenia
  - Steroids (Prednisone)
    - Non-specific inhibitor of T-cells
    - Toxicities include hyperglycemia, hypertension, GI upset, tremors, psychosis
Adult Lung Transplants
Percentage Experiencing TREATED Rejection Between Discharge and 1-Year Follow-Up by Type of Induction (Follow-Ups: July 2004-June 2016)

- No Induction (N=7,153)
- Polyclonal (N=1,415)
- IL-2R Antagonist (N=7,181)
- Alemtuzumab (N=1,168)
Adult Lung Transplants
Percentage Experiencing TREATED Rejection Between Discharge and 1-Year Follow-Up by Maintenance Immunosuppression (Follow-Ups: July 2004-June 2016)

% experiencing treated rejection within 1 year

- CyA + MMF/MPA (N=616)
- CyA + AZA (N=866)
- TAC + MMF/MPA (N=10,840)
- TAC + AZA (N=3,219)
Acute Rejection

- Treatment for ACR
  - Not standardized and lacks conclusive randomized control trials
  - General consensus that rejection episodes grade A2 require treatment
  - Treat symptomatic A1 rejection
  - Asymptomatic A1 rejection can be monitored closely while optimizing immunosuppression

- Medication therapy
  - Methylprednisolone 10-15 mg/kg/day for 3 days
  - Adjust and optimize current immunosuppression regimen
  - Recurrent or persistent rejection (ATG, IL-2R antagonists, or anti-CD52 monoclonal antibody)
  - Continued rejection despite maximal treatment—evaluate for continued trigger
Infections

- HSV and CMV (delayed with prophylaxis)
- Community acquired respiratory viruses
- Aspergillus, Candida, Zygomycoses
- Endemic fungi
  - Pneumocystis jiroveci (delayed with prophylaxis)
- Nosocomial bacteria
- Community acquired bacteria
  - MTB – primary and reactivation of latent infection
  - Non-tuberculous mycobacteria

Months following transplant
Nosocomial infections occur most commonly in the first 6 months post transplant but can occur at any time.

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pseudomonas aeruginosa</td>
<td>25</td>
</tr>
<tr>
<td>Staphylococcus aureus</td>
<td>14</td>
</tr>
<tr>
<td>Acinetobacter baumanii</td>
<td>14</td>
</tr>
<tr>
<td>Escherichia coli</td>
<td>5.3</td>
</tr>
<tr>
<td>Klebsiella pneumonia</td>
<td>5.3</td>
</tr>
<tr>
<td>Stenotrophomonas maltophilia</td>
<td>5.3</td>
</tr>
<tr>
<td>Mycobacterial</td>
<td>5.3</td>
</tr>
<tr>
<td>MTB</td>
<td>3.5</td>
</tr>
<tr>
<td>MAC</td>
<td>1.8</td>
</tr>
</tbody>
</table>
Infections

- **Viral**
  - **Cytomegalovirus**
    - Can cause direct injury (pneumonitis, colitis, gastritis)
    - Indirect injury by
      - Release of pro-inflammatory cytokines that can activate T-lymphocytes and cause graft loss
      - Molecular mimicry to HLA-DR
      - Ongoing graft injury can lead to obliterative bronchiolitis
      - Increases the risk of opportunistic infections that can lead to acute rejection
  - Transplant recipients are risk stratified and post-transplant prophylaxis dependent on risk
    - High risk D+/R-
    - Intermediate D+/R+, D-/R+
    - Low D-/R-
Infections

- **Viral**
  - Community acquired respiratory viruses (CARV)
    - Can be diagnosed by nasopharyngeal/oropharyngeal swabs or BAL
    - Rapid detection PCR panels are becoming more readily available
    - Conflicting evidence associating them with acute rejection and development of BOS
      - Influenza A/B
      - RSV, Parainfluenza, Metapneumovirus
      - Adenovirus, Rhinovirus
Infections

- **Fungal**
  - 70% are caused by molds
    - Aspergillus sp. 45%
  - 30% are caused by yeast
    - Candida sp. 25%
  - 82% of invasive mold infections will involve the lung itself
  - Median timing of is 11 months post transplant

- **Mortality**
  - 3 month mortality after infection is 22-24%
  - 1 year mortality after infection is 44% (non-Aspergillus 60%, Aspergillus 40%)
Post-Transplant >12 Months
Bronchiolitis Obliterans Syndrome

- Sustained (>3 week) decrease in lung function causing chronic obstructive disease
- 25% of lung transplant patients will develop it by two years
- 50% of lung transplant patients will develop it by five years
- Presentation can vary and include
  - Dyspnea with exertion or at rest
  - Cough
  - Recurrent infections (Pseudomonas, Aspergillus)
## Classification system

<table>
<thead>
<tr>
<th>Grade</th>
<th>Pulmonary function</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>FEV1 &gt; 90% of baseline</td>
</tr>
<tr>
<td></td>
<td>FEF 25-75% &gt;75 of baseline</td>
</tr>
<tr>
<td>0p</td>
<td>FEV1 81-90% of baseline</td>
</tr>
<tr>
<td></td>
<td>FEF 25-75% &lt;75 of baseline</td>
</tr>
<tr>
<td>1</td>
<td>FEV1 66-80% of baseline</td>
</tr>
<tr>
<td>2</td>
<td>FEV1 51-65% of baseline</td>
</tr>
<tr>
<td>3</td>
<td>FEV1 &lt;50% of baseline</td>
</tr>
</tbody>
</table>
Bronchiolitis Obliterans Syndrome

![Graph showing FEV₁ % Baseline over time with labels BOS 1, BOS 2, and BOS 3.](chart.png)
Bronchiolitis Obliterans Syndrome

Treatment strategies

- Azithromycin
- Fundoplication
- Enhanced immunosuppression (Alemtuzumab)
- Photopheresis
- Retransplantation
- Palliative care
Malignancies increase over time post lung transplant

- Does not account for significant mortality

<table>
<thead>
<tr>
<th>Malignancy/Type</th>
<th>1-Year Survivors</th>
<th>5-Year Survivors</th>
<th>10-Year Survivors</th>
</tr>
</thead>
<tbody>
<tr>
<td>No Malignancy</td>
<td>21,701 (94.8%)</td>
<td>8,073 (80.9%)</td>
<td>2,087 (69.4%)</td>
</tr>
<tr>
<td>Malignancy (all types combined)</td>
<td>1,187 (5.2%)</td>
<td>1,905 (19.1%)</td>
<td>921 (30.6%)</td>
</tr>
<tr>
<td>Malignancy Type*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Skin</td>
<td>403</td>
<td>1347</td>
<td>692</td>
</tr>
<tr>
<td>Lymphoma</td>
<td>239</td>
<td>146</td>
<td>71</td>
</tr>
<tr>
<td>Other</td>
<td>515</td>
<td>518</td>
<td>245</td>
</tr>
<tr>
<td>Type Not Reported</td>
<td>30</td>
<td>12</td>
<td>1</td>
</tr>
</tbody>
</table>
ECMO and Lung Transplantation
ECMO Getting More Mobile and Versatile
ECMO Over Time

1960

1972
First reported use of ECMO for extracorporeal life support by Donald Hill

1975
ECMO use extended as bridge to transplant

Development of heparin-coated circuits and centrifugal pumps over traditional roller pumps

New innovations in polymethylpentene (PMP) oxygenators

Extensive use of dual lumen avalon cannula

Present

2006
CESAR Trial

2009
H1N1 influenza outbreak

Increasing use of ECMO as a transplant bridge due to advancements in technology and institution experiences

limited ECMO use as a bridge to transplant due to poor outcomes from various prospective studies
Types of ECMO

- Veno-venous ECMO (vvECMO)
  - Has venous drainage and venous return
  - Uses peripheral cannulation
  - Major indication is primary respiratory failure

- Veno-arterial ECMO (vaECMO)
  - Venous drainage with arterial return
  - Can utilize peripheral or central cannulation
  - Mode of choice when there is cardiogenic shock/hemodynamic instability
ECMO for Lung Transplantation

- Has different indications for lung transplantation
  - Bridging with ECMO to lung transplantation
  - Intraoperative ECMO during lung transplantation
  - Postoperative ECMO as rescue therapy after lung transplantation
ECMO for Bridging to Lung Transplant

- ISHLT Consensus Statement on ECMO as a bridge to transplant
  - Recommended for
    - Young patients
    - In patients with the absence of multi-organ dysfunction
    - Good potential for rehabilitation
  - Not recommended for
    - Septic shock
    - Multi-organ dysfunction
    - Severe arterial occlusive disease
    - HIT
    - Prior prolonged mechanical ventilation
    - Advanced age
    - Obesity
Should lung transplantation be performed for patients on mechanical respiratory support? The US experience

David P. Mason, MD, a Lucy Thuita, MS, b Edward R. Nowicki, MD, MS, a Sudish C. Murthy, MD, PhD, a Gösta B. Pettersson, MD, PhD, a and Eugene H. Blackstone, MD a,b
Extracorporeal membrane oxygenation as a bridge to lung transplantation may not impact overall mortality risk after transplantation: results from a 7-year single-centre experience

Fabio Ius, Ruslan Natanov, Jawad Salman, Christian Kuehn, Wibeke Sommer, Murat Avsar, Thierry Siemeni, Dmitry Bobylev, Reza Poyanmehr, Dietmar Boethig, Joerg Optenhoevel, Nicolas Schwer, Axel Haverich, Gregor Warnecke and Igor Tudorache

Department of Cardiothoracic, Transplant and Vascular Surgery, Hannover Medical School, Hannover, Germany

German Center for Lung Research (DZL/BMWFU), Gelsen, Hannover, Germany

Department of Paediatrics, Hannover Medical School, Hannover, Germany

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Figure 2: Graft survival that was similar among patients who require pretransplant ECMO (red line) and patients who did not require pretransplant ECMO (blue line) (P = 0.13) is shown. ECMO: extracorporeal membrane oxygenation.
# ECMO as a Bridge to Lung Transplant

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Patients</th>
<th>1-y surv</th>
<th>Comment, transplant center, etc</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aigner et al</td>
<td>2007</td>
<td>2</td>
<td>n/a</td>
<td>Vienna</td>
</tr>
<tr>
<td>Broome et al</td>
<td>2008</td>
<td>1</td>
<td>n/a</td>
<td>On ECMO 58d before LTx, Gothenburg</td>
</tr>
<tr>
<td>Mason et al</td>
<td>2010</td>
<td>51</td>
<td>62%</td>
<td>UNOS data, USA experience 1987-2008</td>
</tr>
<tr>
<td>Hämmäinen et al</td>
<td>2011</td>
<td>13</td>
<td>92%</td>
<td>ITT ECMO 75% 1y, Gothenburg and Helsinki</td>
</tr>
<tr>
<td>Haneya et al</td>
<td>2011</td>
<td>7</td>
<td>?</td>
<td>5/7 d/c hospital, Regensburg, Germany</td>
</tr>
<tr>
<td>Toyoda et al</td>
<td>2013</td>
<td>24</td>
<td>74%</td>
<td>No surv diff compared to non-ECMO, Pittsburgh</td>
</tr>
<tr>
<td>Lang et al</td>
<td>2014</td>
<td>12</td>
<td>50%</td>
<td>Awake better 1y surv, only re-Ltx, Vienna</td>
</tr>
<tr>
<td>Lehmann et al</td>
<td>2015</td>
<td>13</td>
<td>71%</td>
<td>No surv diff compared to non-ECMO, Leipzig</td>
</tr>
<tr>
<td>Dellgren et al</td>
<td>2015</td>
<td>16</td>
<td>75%</td>
<td>ITT ECMO 62% 1y Surv, Gothenburg</td>
</tr>
<tr>
<td>Hayanga et al</td>
<td>2016</td>
<td>342</td>
<td>62-81%</td>
<td>UNOS data 2000-2014, low vs hi volume centers</td>
</tr>
<tr>
<td>Hoetzenecker et al</td>
<td>2018</td>
<td>63</td>
<td>76%</td>
<td>Including 9 with Novalung, re-LTx worse survival, Toronto</td>
</tr>
<tr>
<td>Ius et al</td>
<td>2018</td>
<td>68</td>
<td>79%</td>
<td>7% of all, No surv diff compared to non-ECMO, Hannover</td>
</tr>
</tbody>
</table>
ECMO During Lung Transplantation

- Mechanical circulatory support during lung transplant is not always needed

- Factors used to determine the need for intra-operative mechanical circulatory support
  - Surgical approach
    - Sternotomy will require cardiopulmonary bypass
  - RV function
  - Degree of pulmonary HTN
  - Ability of the patient to tolerate single lung ventilation and clamping of the contralateral pulmonary circulation
ECMO During Lung Transplantation

- **Cardiopulmonary bypass**
  - **Pros:** Allows complete unloading and aortic clamping if needed
  - **Cons:** Requires full heparinization, may be associated with higher risk of PGD, requires sternotomy or clamshell surgical approach

- **ECMO**
  - **Pros:** Partial heparinization, easy access via peripheral or central cannulation, support can continue in the ICU, possibly less bleeding, possibly less PGD
  - **Cons:** More demanding for anesthesia, no blood suction back into the system
### ECMO During Lung Transplant

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>ECMO/vs CPB</th>
<th>1-y surv</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aiger et al</td>
<td>2007</td>
<td>130/27</td>
<td>74%/66%</td>
<td>No difference in survival, Vienna</td>
</tr>
<tr>
<td>Bittner et al</td>
<td>2007</td>
<td>8/7</td>
<td>50%/85%</td>
<td>Lower survival ECMO vs CPB, Leipzig</td>
</tr>
<tr>
<td>Ius et al</td>
<td>2012</td>
<td>46/46</td>
<td>81%/59%</td>
<td>Lower survival and more compl in CPB, Hannover</td>
</tr>
<tr>
<td>Bermudez et al</td>
<td>2014</td>
<td>49/222</td>
<td>81%/81%</td>
<td>Fewer compl in ECMO group, Pittsburgh</td>
</tr>
<tr>
<td>Biscotti et al</td>
<td>2014</td>
<td>47/55</td>
<td>92%/84%</td>
<td>Fewer compl and less PGD in ECMO group, New York</td>
</tr>
<tr>
<td>Hoechter et al</td>
<td>2015</td>
<td>27/22</td>
<td>81%/81%</td>
<td>Munich</td>
</tr>
<tr>
<td>Machuca g et al</td>
<td>2015</td>
<td>33/66</td>
<td>N/A</td>
<td>No diff in surv, less compl in ECMO group, Toronto</td>
</tr>
<tr>
<td>Ius et al</td>
<td>2016</td>
<td>170/425 (no MCS)</td>
<td>N/A</td>
<td>No diff in surv, more compl in ECMO group, Hannover</td>
</tr>
<tr>
<td>Cosgun et al</td>
<td>2018</td>
<td>134/157 (no MCS)</td>
<td>84%/90%</td>
<td>No diff in surv, more compl in ECMO group, Zurich</td>
</tr>
</tbody>
</table>
ECMO During Lung Transplant

- Caveats for ECMO based on surgical approach
  - Clamshell
    - Requires central vaECMO
  - Thoracotomy
    - Can use peripheral cannulation or combination of peripheral/central cannulation for ECMO
  - Sternotomy
    - Requires cardiopulmonary bypass
    - ECMO does not fully unload the heart from this approach
Indications for ECMO Post Lung Transplant

- vvECMO for signs of PGD 3
  - Increased airway pressures
  - Requiring high FiO2 with low pO2 <300

- vvECMO used intraoperatively then continued postoperatively
  - If vaECMO used then should try to convert to vvECMO before going to the ICU
Those that require ECMO post lung transplantation have worse outcomes than those that don’t require ECMO.
<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Rate</th>
<th>%</th>
<th>1-y surv</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glassman et al</td>
<td>1995</td>
<td>16/215</td>
<td>7.4</td>
<td>?</td>
<td>7/16 d/c home, Pittsburgh</td>
</tr>
<tr>
<td>Meyers et al</td>
<td>2000</td>
<td>12/444</td>
<td>2.7</td>
<td>?</td>
<td>7/12 d/c home, St Louis</td>
</tr>
<tr>
<td>Nguyen et al</td>
<td>2000</td>
<td>14/253</td>
<td>5.5</td>
<td>?</td>
<td>5/14 d/c home, Mayo</td>
</tr>
<tr>
<td>Oto et al</td>
<td>2004</td>
<td>10/481</td>
<td>2.2</td>
<td>?</td>
<td>3/10 d/c home, Melbourne</td>
</tr>
<tr>
<td>Aigner et al</td>
<td>2007</td>
<td>22/306</td>
<td>7.2</td>
<td>53%</td>
<td>Vienna</td>
</tr>
<tr>
<td>Bermudez et al</td>
<td>2009</td>
<td>58/763</td>
<td>7.6</td>
<td>40%</td>
<td>Pittsburgh</td>
</tr>
<tr>
<td>Hartwig et al</td>
<td>2012</td>
<td>28/498</td>
<td>5.6</td>
<td>64%</td>
<td>Duke</td>
</tr>
<tr>
<td>Bittner et al</td>
<td>2012</td>
<td>6/108</td>
<td>5.6</td>
<td>33%</td>
<td>Leipzig</td>
</tr>
<tr>
<td>Mulvihill et al</td>
<td>2016</td>
<td>107/2098</td>
<td>5.1</td>
<td>N/A</td>
<td>UNOS, USA collective 2015-2016</td>
</tr>
</tbody>
</table>
Thank You For Your Attention