Lung Transplantation in Patients with Cystic Fibrosis

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NUMBER OF LUNG TRANSPLANTS REPORTED
BY YEAR AND PROCEDURE TYPE

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.
ADULT LUNG RECIPIENTS
Cross-Sectional Analysis
Functional Status of Surviving Recipients
(Follow-ups: April 1994 – June 2009)
Lung Transplantation
Procedure Options

• **Double-lung transplantation**
  – Donor hearts could serve other patients
  – Avoids risk of accelerated atherosclerosis

• **Heart-lung transplantation**
  – Less commonly performed in the US
  – Fewer airway complications

• **Bilateral living lobar transplantation**
  – Reduced incidence and intensity of rejection
  – Circumvents the donor shortage problem
  – Considerable risk to donors

• **Split-lung transplantation**
  – Single donor can serve multiple recipients
  – Technically difficult procedure

Double-Lung Transplantation

Photos courtesy of Woo MS.
CF and Lung Transplant

- The course of CF is very unpredictable, and that makes the timing for transplant more difficult
- About 1600 CF recipients since 1991
- 120-150 recipients each year
- Second largest group to get transplanted
- CF recipients do better in general than non-CF recipients
Transplantation Window of Opportunity—in an Ideal World


“Transplant window”

Clinical course

Time

TOO SOON

TOO LATE

Too Soon

Too Late
Transplantation Window of Opportunity—in Reality

“Transplant window??”

Time

Clinical course

TOO SOON?

TOO LATE?
Difficult Questions to Ask Before Organ Transplantation

• When should a patient be referred for evaluation?
• When should a patient be placed on the waiting list?
• When should a patient have a transplant?
Referral for Lung Transplant

- Patient readiness
- Transplant team readiness and comfort level
- Local transplant center culture
- Wait times (less important now because of LAS)
Lung Allocation Score

- New scoring system since May 2005
- “How bad you need it + How well you’ll do with it”
- Applies to transplant candidates > 12 yrs
- Scores range from 0-100
- Scores can be updated
<table>
<thead>
<tr>
<th>Clinical Information</th>
<th>Lung Allocation Score:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diagnosis</td>
<td>PASP</td>
</tr>
<tr>
<td>Age</td>
<td>PCWP</td>
</tr>
<tr>
<td>Height and Weight</td>
<td>FVC</td>
</tr>
<tr>
<td>(BMI)</td>
<td>Serum Creatinine</td>
</tr>
<tr>
<td>Diabetes</td>
<td>Functional Status</td>
</tr>
<tr>
<td>Use of supplemental</td>
<td>Assisted Ventilation</td>
</tr>
<tr>
<td>oxygen</td>
<td></td>
</tr>
<tr>
<td>Six minute walk</td>
<td></td>
</tr>
<tr>
<td>distance</td>
<td></td>
</tr>
</tbody>
</table>
Lung Allocation Score: 

**CF Variables That Are Not Included**

- $\text{FEV}_1$
- $\text{pCO}_2$
- Infections
- Antibiotic Sensitivity of Infections
- Hemoptysis
- Frequency of Exacerbations
The Kerem Survival Model

Significant predictors of 2-year survival

Single covariate analysis

- $\text{FEV}_1$ and $\text{FVC}$
- Female gender
- Low arterial $\text{pO}_2$
- High arterial $\text{pCO}_2$
- Low weight-for-height

Multiple covariate analysis

- $\text{FEV}_1$
- Female gender
- Age

Consensus Guidelines for Referral of Lung Transplant Candidates with CF

- \( \text{FEV}_1 \leq 30\% \) of predicted with rapid, progressive respiratory deterioration
  - Increasing number of hospitalizations
  - Massive hemoptysis
  - Recurrent pneumothorax
  - Increasing cachexia
  - Rapid fall in \( \text{FEV}_1 \)
- Hypoxemia: \( \text{PaO}_2 < 55 \text{ mm Hg} \)
- Hypercapnia: \( \text{PaCO}_2 > 50 \text{ mm Hg} \)
- <50% survival in 2 years
- Early referral is recommended for young female patients, who have particularly poor prognosis

# The Validated Predictive 5-Year Survival Model of CF

<table>
<thead>
<tr>
<th>Increased survival:</th>
<th>FEV₁ % equivalency*</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Pancreatic sufficiency</td>
<td>+12</td>
</tr>
<tr>
<td>• Higher weight-for-age z-score</td>
<td>+10</td>
</tr>
<tr>
<td>• <em>Staphylococcus aureus</em> infection</td>
<td>+6</td>
</tr>
<tr>
<td>• Higher FEV₁%</td>
<td>+1</td>
</tr>
<tr>
<td><strong>Decreased survival:</strong></td>
<td></td>
</tr>
<tr>
<td>• <em>Burkholderia cepacia</em> infection</td>
<td>−48</td>
</tr>
<tr>
<td>• Diabetes mellitus</td>
<td>−13</td>
</tr>
<tr>
<td>• Acute pulmonary exacerbation</td>
<td>−12</td>
</tr>
<tr>
<td>• Female gender</td>
<td>−6</td>
</tr>
<tr>
<td>• Increasing age</td>
<td>−0.7</td>
</tr>
</tbody>
</table>

*Difference in FEV₁ (% predicted) required for equivalent effect on survival

Equivocal Survival Benefit of Lung Transplantation in Patients with FEV$_1$ ≤30%

Predicting the “Right Time” for Transplant

- Study to look at who was listed too late
- Evaluated who was listed for transplant but died before receiving new lungs
- Rationale is that there are things that the transplant centers integrate with the variables collected by the CFF Registry and UNOS
- Four transplant centers

Belkin et al. AJRCCM 2006
Predicting the “Right Time” for Transplant

Variables that increased risk of death
- $\text{FEV}_1 < 30\%$ predicted
- Shorter height
- $\text{P}_a\text{CO}_2 > 50\text{mmHg}$
- Need for nutritional intervention

Variables that decreased risk of death
- Referral from a CF Center
- Listing after 1996

Belkin et al. AJRCCM 2006
Guidelines for referral:
- FEV\(_1\) below 30% predicted or a rapid decline in FEV\(_1\)
  - in particular young female patients
- Exacerbation of pulmonary disease requiring ICU stay
- Increasing frequency of exacerbations requiring abx
- Refractory/recurrent pneumothorax
- Recurrent hemoptysis not controlled by embolization
International Guidelines for the Selection of Lung Transplant Candidates: 2006 Update

• Guidelines for transplant:
  – Oxygen-dependent respiratory failure
  – Hypercapnia
  – Pulmonary hypertension
Absolute Contraindications to Lung Transplantation

Active malignancy <5 years

- Infections affecting long-term survival
  - HIV
  - Hepatitis B or C
  - Tuberculosis

- Other major organ dysfunction
  - Cardiovascular disease
  - Liver disease: hepatitis C
  - Renal failure: Cl$_{Cr}$ <50 mL/min
  - Other organ damage

Relative Contraindications to Lung Transplantation

- Symptomatic osteoporosis
- CF-related arthropathy
- Pan-resistant organisms
- Kyphoscoliosis
- Fungi or atypical mycobacteria
- High-dose corticosteroid use
- Invasive ventilation
- Nutritional status (<70% or >130% IBW)
- Psychosocial problems
- Substance addiction

Postoperative Issues specific to CF Lung Transplant Recipients
Excess Mortality Associated with Preoperative *B cepacia* Infection

Post-transplant Survival Influenced by *B cepacia* Genomovar Type

<table>
<thead>
<tr>
<th>Study</th>
<th>Genomovar III</th>
<th>Non-genomovar III</th>
<th>P value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aris</td>
<td>5</td>
<td>0</td>
<td>0.035</td>
</tr>
<tr>
<td>De Soyza</td>
<td>4</td>
<td>0</td>
<td>0.007</td>
</tr>
</tbody>
</table>

*Genomovar III vs non-genomovar III

Lung Transplantation in Adult CF Patients with History of Acute Respiratory Failure

N = 42
Admitted to ICU with hypercapnic respiratory failure

n = 17 (40%)
Received lung transplants

n = 14 (82%)
Alive at 1 year postoperation

n = 19 (45%)
Died in ICU

n = 3 (7%)
Died within 6 months of ICU discharge

n = 3 (7%)
Alive at 1 year without lung transplant

## Potential Surgical Complications of Lung Transplantation

<table>
<thead>
<tr>
<th>Complication</th>
<th>Prevalence (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Most serious</strong></td>
<td></td>
</tr>
<tr>
<td>• Primary graft failure due to ischemia-reperfusion injury/diffuse alveolar damage</td>
<td>15-35</td>
</tr>
<tr>
<td>• Anastomotic complications: vascular or airway</td>
<td>7</td>
</tr>
<tr>
<td><strong>Most common</strong></td>
<td></td>
</tr>
<tr>
<td>• Phrenic/vocal cord paresis</td>
<td>3-30</td>
</tr>
<tr>
<td>• Gastroparesis</td>
<td>25-30</td>
</tr>
</tbody>
</table>
Potential Medical Complications Following Lung Transplantation

- Obliterative bronchiolitis (BOS/chronic rejection)
- Acute rejection
- Infection: viral, bacterial, fungal, protozoal
- Toxicity of immunosuppressives
  - Nephrotoxicity
  - Hypertension
  - Hirsutism, gingival hyperplasia
- Diabetes
- Hyperlipidemia
- Post-transplant lymphoproliferative disease (EBV)

Recommended Follow-up of Transplant Recipients

- Regular monitoring of PFTs, chest x-rays, and blood tests
  - Creatinine, complete blood count, liver function tests, CMV infection
- Post-transplant bronchoscopy; surveillance with BAL and transbronchial biopsy following:
  - Decline in PFTs
  - Change in chest x-ray
  - Onset of new symptoms
  - Acute rejection

Photo courtesy of Woo MS.
Special Issues for the CF Patient

- Colonization vs. infection
- Sinus disease
- GI Issues:
  - GERD
  - Pancreatic Insufficiency
  - Nutrition
  - DIOS
- CFRD
- Osteoporosis
- Psychosocial
French Lung Transplant Experience for CF

- Compared two five year periods (2000-2005 and 2005-2010)
  - Improved one year survival (75% to 88%) due to: extensive use of thoracic epidurals leading to increased early extubations

Mordant et al. European Journal of Cardiothoracic Surgery. 2010
Survival of Transplant Recipients by Procedure Type

Survival (%)

Bilateral lung (N = 6686)
Single lung (N = 8581)
All lungs (N = 15,267)

Years

Causes of Death in Lung Transplant Recipients

- Technical complication
- Graft failure
- Cardiovascular disease
- Infection – Non-CMV
- Chronic rejection
- Malignancy – Non-lymphoma

<table>
<thead>
<tr>
<th>Time after transplantation</th>
<th>Percent of deaths</th>
</tr>
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<tbody>
<tr>
<td>0-30 days</td>
<td></td>
</tr>
<tr>
<td>31 days - 1 year</td>
<td></td>
</tr>
<tr>
<td>&gt;1-3 years</td>
<td></td>
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<tr>
<td>&gt;3-5 years</td>
<td></td>
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<tr>
<td>&gt;5 years</td>
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Summary

• CF is the third most common indication for lung transplant
• Decision of transplantation is derived from a comprehensive evaluation that MUST take into account several indicators of disease severity: FEV$_1$, increase in O$_2$ need, hypercapnia, need for non-invasive ventilation, functional status & pulmonary hypertension.
Summary

• Post-transplant survival of CF patients is similar or even greater than survival of patients with other conditions