Transplanting Interstitial Lung Disease

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Disclosures

I have nothing to disclose

Adult Lung Transplants
Number of Transplants by Year and Procedure Type

Lung Transplantation
Indications

- A consensus document for the selection of lung transplant candidates 2014. J Heart Lung Transplant
- Chronic advanced lung disease
- Failed medical management
- Primary goal is improved duration of life but improved quality of life is also a consideration
- For most patients the ultimate “treatment” rather than cure
- Trading one medical condition for another
Lung Transplantation

Disease Indications

- Pulmonary Vascular Disease
  - PAH
  - PH secondary to systemic disease
  - Eisenmenger’s syndrome
- Obstructive Lung Disease
  - Smoking related
  - A1ATd
- Suppurative Lung Disease
  - Cystic Fibrosis
  - Bronchiectasis
- Restrictive Lung Disease
  - IPF
  - NSIP
  - Sarcoidosis
  - Eosinophilic granuloma
  - LAM
  - Occupational lung disease
  - Hypersensitivity pneumonitis
  - Bronchiolitis obliterans

UCSF Transplant Recipient Characteristics

<table>
<thead>
<tr>
<th>Condition</th>
<th>UCSF</th>
<th>Region</th>
<th>US</th>
</tr>
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<tbody>
<tr>
<td>PAH</td>
<td>0</td>
<td>4.0</td>
<td>3.6</td>
</tr>
<tr>
<td>CF</td>
<td>11.1</td>
<td>14.2</td>
<td>12.3</td>
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<tr>
<td>IPF</td>
<td>77.8</td>
<td>61.0</td>
<td>53.8</td>
</tr>
<tr>
<td>COPD</td>
<td>11.1</td>
<td>18.5</td>
<td>27.5</td>
</tr>
<tr>
<td>Other</td>
<td>0</td>
<td>2.3</td>
<td>2.8</td>
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</table>

Lung Allocation Score

- Implemented May 2005
- Way to determine who receives donor lungs based on medical urgency and probability of success
- Based on medical testing completed during evaluation
- Also based on diagnosis, favoring ILD and CF (have highest risk on waiting list)
- Electronic listing
- Repeat specified tests every 6 months
LAS Calculation

Waiting List Urgency Parameters

- Age
- $O_2$ requirement at rest
- BMI
- DM
- Dx
- 6 MWD < 150 ft
- Functional Status
- Mechanical ventilation
- FVC
- $PaCO_2$

Post Tx Survival

- Age
- Mechanical Ventilation
- Functional Status
- Dx
- PCWP
- FVC
- $PaCO_2$

Lung Allocation Score


Lung Allocation Score Predicts Survival in Lung Transplantation Patients With Pulmonary Fibrosis

Pulmonary Fibrosis Pre-LAS

The Annals of Thoracic Surgery

Volume 88, Issue 6, December 2009, Pages 1757–1764
Timing of Referral
General Recommendations

- Early referral is highly desirable
- Consider when patient is symptomatic during daily activities (NYHA III or IV)
- When expected survival is 2-3 years
- Aids in the psychology of accepting and confronting life-threatening illness
- Aids in actively managing end-stage illness

Referral Guidelines
- UIP
- Fibrotic NSIP
- Oxygen requirement
- DLCO < 40%

Listing Guidelines
- 10% drop in FVC over 6 months
- 15% drop in DLCO over 6 months
- Desaturation with 6MWT or drop in 6MWT distance
- Pulmonary hypertension or hospitalization

Pulmonary Fibrosis
Disease Specific Guidelines

If IPF, REFER EARLY

Pulmonary Fibrosis and Pancytopenia

- 56 y/o female presents to UCSF in 2/2009 with complaints progressive non-productive cough
- Cough progressive over the course of 3-4 years
- Notes mild dyspnea on exertion, though is able to exercise for 30 minutes on an elliptical machine
- No other systemic symptoms such as arthralgias, myalgias, rashes or photosensitivity
Pulmonary Fibrosis and Pancytopenia

- **PMHx:**
  - Lyme Disease in 2004. She was noted to have a mild pancytopenia at that time – thought to be related
- **FHx:**
  - Mother was diagnosed with pulmonary fibrosis at the age of 55 and died at 60. She had possible lupus.
  - Sister has asthma
- **SHx:** no exposures

DATA

- **PFTs:**
  - TLC 4.11 (76%)
  - FVC 2.83 (76%)
  - FEV1 2.31 (80%)
  - DLCO 15.33 (55%)
- **CBC:**
  - WBC 3,200
  - HCT 32.0
  - PLT 73,000

Pulmonary Fibrosis and Pancytopenia

- Started on Perfenidone through a trip to Europe
- By 2011 dyspnea became the prominent problem
- She was now hypoxic and using oxygen with both rest and exertion
- PFTs show a progression
  - TLC 2.85 (52%)
  - FVC 1.68 (46%)
  - DLCO 10.49 (38%)
- FHx – sister previously thought to have asthma now diagnosed with Hypersensitivity Pneumonitis
Referred for Lung Transplant Evaluation

Hematology Evaluation:
- BM Biopsy 5/27/2011
  - Hypocellular marrow for age with mixed hematopoiesis and blasts less than 5%
  - Borderline/minimal normochromic and normocytic anemia and thrombocytopenia
- Diagnosis: Mild aplastic anemia

FHx: Sister now has undergone lung transplant. She developed significant hematologic problems post transplant including thrombocytopenia

What test would help explain the cause of this patients progressive pulmonary fibrosis and pancytopenia?

- Telomerase mutation genetic analysis was performed
- This revealed a sequence variant in the TERC gene
**Pulmonary Fibrosis and Pancytopenia**
- Patient underwent double lung transplant
- Post-operative course complicated by thrombocytopenia into the 20,000s
- Platelets gradually recovered to her baseline of 80-90,000
- Her sister, transplanted at another center is also doing well

**Familial Fibrosis and Lung Transplantation**
- Retrospective case series of 14 lung transplant recipients with telomerase complex mutations
- All had fibrotic lung disease but only 43% had UIP pattern on CT imaging
- High incidence of cytopenias, particularly leukopenia, post transplantation (83%)
- Of these, 5 could not tolerate anti-proliferative agents – but not associated with acute rejection or CLAD
- CLAD occurred in 33% of recipients at median 3.1 years

**Hypersensitivity Pneumonitis**
- Rare, progressive ILD triggered by inhaled antigens
- Primary treatment is removal of antigen from environment
- Offending agent only ID’d in 40% of cases
- A subset of patients develop progressive fibrosis
- Can Lung Transplantation help this group?
- What is the outcome including survival?
- Does it recur?

**Hypersensitivity Pneumonitis**
- Retrospective cohort study of 31 patients transplanted for HP between 2001-2013
- 12 of 31 had known inciting exposure (39%)
- 5 of the 31 had diagnosis of IPF prior to transplant
Hypersensitivity Pneumonitis

- 2 of the 31 patients developed recurrent HP
- Both cases were associated with:
  - Exposure to presumed antigen
  - Granulomas on biopsy
  - Drop in lung function
  - No infectious cause
  - Improvement/stabilization with treatment with steroids

Hypersensitivity Pneumonitis

CTD related ILD
**Adult Lung Transplantation: Indications**

<table>
<thead>
<tr>
<th>DIAGNOSIS</th>
<th>SLT (N = 12,339)</th>
<th>BLT (N = 18,334)</th>
<th>TOTAL (N = 30,673)</th>
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<tbody>
<tr>
<td>idiopathic Pulmonary Fibrosis</td>
<td>3,995 (32.4%)</td>
<td>2,038 (10.8%)</td>
<td>6,033 (22.6%)</td>
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<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>Pulmonary Fibrosis, Other</td>
<td>424 (3.4%)</td>
<td>537 (2.9%)</td>
<td>961 (3.1%)</td>
</tr>
<tr>
<td>sarcoidiosis</td>
<td>236 (1.9%)</td>
<td>547 (3.0%)</td>
<td>783 (2.6%)</td>
</tr>
<tr>
<td>Connective Tissue Disease</td>
<td>137 (1.1%)</td>
<td>232 (1.3%)</td>
<td>369 (1.2%)</td>
</tr>
<tr>
<td>LAM</td>
<td>101 (0.8%)</td>
<td>207 (1.1%)</td>
<td>308 (1.0%)</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>Other</td>
<td>108 (0.9%)</td>
<td>291 (1.6%)</td>
<td>399 (1.3%)</td>
</tr>
</tbody>
</table>

**Pulmonary Fibrosis**

Collagen Vascular Diseases

- Associated with: Scleroderma, Rheumatoid arthritis, Mixed connective tissue disease, Dermatomyositis
- Each patient should have individual consideration
- Evidence of quiescent systemic disease is desired
- Active vasculitis is a contraindication

**Freedom from BOS**

Scleroderma vs. IPF

**Lung Transplant Survival**

Scleroderma vs IPF
Scleroderma and Aspiration Risk

- Severe pulmonary fibrosis (FVC and DLCO <40%), unresponsive to medical treatment
- Creatinine clearance above 60 mL/min
- Absence of severe skin involvement (severe cutaneous thickening)
- Absence of severe esophageal dysmotility and aspiration
- Absence of significant conduction abnormalities
- Absence of severe small intestine, gastroparesis, colorectal and rectum involvement such as pseudo-obstruction, diverticulitis, and perforation

What about patients who are referred late or who have acute illness?
IPF Exacerbation

- Acute Deterioration associated with right heart strain
- Intubation can make worse (positive pressure ventilation)
- Traditionally lung transplantation has not been an option for those with respiratory failure
- Reluctance because of concern for dismal outcome
- Allocation of lungs (based on time on wait list)
- Experience with ECLS and MV as well as change in LAS have shifted this paradigm


Case IPF Exacerbation

- 55 y/o male presents with acute worsening of chronic dyspnea
- CT shows new GGO in addition to chronic ILD
- Progressive hypoxic respiratory failure
- Taken to OR for placement on ECLS (ECMO)

ECMO: PERMITS AMBULATION PRE-TRANSPLANTATION!!

31 patients bridged to transplant using ECMO
- 93% survival at 1 year
- 80% survival at 3 years
- 66% survival at 5 years

UCSF Experience
ECMO Bridge to Transplant

SCHOOL OF MEDICINE * UNIVERSITY OF CALIFORNIA, SAN FRANCISCO

ECMO as Bridge to Transplant Outcomes

- 34 patients bridged with ECMO to lung transplantation
- 26/34 patients survived to discharge
- Survival (conditional 3 month) at 1,3 and 5 years was the same between the ECMO group and controls

Consensus
ECMO Bridge to Transplant

- Recommended
  - Young age
  - Absence of multiple organ dysfunction
  - Good potential for rehabilitation

- Not Recommended
  - Septic shock
  - Multi-organ dysfunction
  - Severe arterial occlusive disease
  - HIT
  - Prior prolonged mechanical ventilation
  - Advanced age and Obesity

Donor Lungs Too Frequently Rejected

- Present criteria exclude more than 85% of lungs
- 29 pairs of rejected lungs were assessed by physiological, microbiological, and histological methods
- 83% had no or mild pulmonary edema, 74% intact alveolar fluid clearance, and 62% normal or mildly abnormal histological findings
- 41% of rejected lungs would have been potentially suitable for transplantation

Ex-vivo Lung Perfusion “Lung in a Box”

**Ex-vivo Lung Perfusion**

- **INSPIRE trial**
  - RCT comparing preservation with OCS to cold flush and storage

- **EXPAND trial**
  - To evaluate the safety and effectiveness of OCS for assessing expanded criteria donor lungs

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### Kaplan-Meier Survival By Diagnosis

**ADULT LUNG TRANSPLANTATION**

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

- **Alpha-1** (N=2,349)
- **CF** (N=4,828)
- **COPD** (N=10,741)
- **IPF** (N=45,476)
- **Sarcoidosis** (N=756)

**Kaplan-Meier Survival By Era**

**ADULT LUNG TRANSPLANTATION**

**Kaplan-Meier Survival by Era** (Transplants: January 1988 – June 2009)

- **1988-1994** (N=4,549)
- **1995-1999** (N=6,765)
- **2000-6/2009** (N=20,728)

Survival comparisons by era:
- **1988-94 vs. 1995-99**: p = 0.4858
- **1988-94 vs. 2000-6/09**: p < 0.0001
- **1995-99 vs. 2000-6/09**: p < 0.0001
IMPROVED QUALITY OF LIFE

"I couldn't even walk to the bathroom 3 1/2 months ago," she said. "The fact I can walk and talk for 5 miles is amazing. A month ago, I didn't think I could do this."

Summary

- Lung Transplant is often the final therapy option for Interstitial Lung Disease
- Early referral is important component of favorable outcomes
- The Lung Allocation Score decreases waiting time and aims to decrease death on waiting list
- Using novel techniques such as ECLS, emergent lung transplant is possible for otherwise good candidates
- Donor availability remains a limiting factor
- Using novel technologies, we may have more donor lungs available, further decreasing the risk of death on the waiting list

Thank you

Questions?

Lung Transplant Referrals: (415) 353-4145