Clinical Updates in Lung Transplantation: Emerging Therapeutic Options

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Disclosures

I have nothing to disclose
Number of Transplants by Type per Year

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

Lung Transplant
Major Indications By Year

- CF
- IPF
- COPD
- Alpha-1
- IPAH
- Re-Tx

% of Transplants

Transplant Year

JHLT. 2013 Oct; 32(10): 965-978
UCSF Transplant Recipient Characteristics

<table>
<thead>
<tr>
<th>Condition</th>
<th>UCSF</th>
<th>Region</th>
<th>US</th>
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</thead>
<tbody>
<tr>
<td>PAH</td>
<td>8.7</td>
<td>5.8</td>
<td>5.5</td>
</tr>
<tr>
<td>CF</td>
<td>8.7</td>
<td>14.0</td>
<td>14.5</td>
</tr>
<tr>
<td>IPF</td>
<td>65.2</td>
<td>47.5</td>
<td>45.8</td>
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<tr>
<td>COPD</td>
<td>17.4</td>
<td>31.9</td>
<td>29.9</td>
</tr>
<tr>
<td>Other</td>
<td>0</td>
<td>0.8</td>
<td>4.2</td>
</tr>
</tbody>
</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
- O2 requirement at rest
- BMI
- DM
- Dx
- 6 MWD < 150 ft
- Functional Status
- Mechanical ventilation
- FVC
- PaCO2
- PAP

### Post Tx Survival
- Age
- Mechanical Ventilation
- Functional Status
- Dx
- PCWP
- FVC
- PaCO2

## Lung Allocation Score

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

Pulmonary Fibrosis

Pre-LAS
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
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...
Pulmonary Fibrosis and Pancytopenia

Referred for Lung Transplant Evaluation

Hematology Evaluation:

- BM Biopsy 5/27/2011
  - Hypocellular marrow for age with mixed hematopoesis 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 patient’s 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 (1/1995-6/2010)

<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>Sarcoidosis</td>
<td>236 (1.9%)</td>
<td>547 (3.0%)</td>
<td>783 (2.6%)</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>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>

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**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

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*J Heart Lung Transplant. 2011 Oct; 30 (10): 1071-1132*
Freedom from BOS
Scleroderma vs. IPF

Number at risk
Scleroderma
-3-2-1-0-1-2-3-4-5
0 1 2 3 4 5
Freedom from Bronchiolitis Obliterans Syndrome

Lung Transplant Survival
Scleroderma vs IPF

Overall Survival

Number at risk
Scleroderma
-3-2-1-0-1-2-3-4-5
0 1 2 3 4 5

Scleroderma and Aspiration Risk
Scleroderma Evaluation

- 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)

Acute Interstitial Pneumonia
(AIP)
ECMO: 

ECMO: PERMITS AMBULATION PRE-
TRANSPLANTATION!!

UCSF Experience
ECMO Bridge to Transplant

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

Stig Steen, Transplantation of Lungs From Non–Heart-Beating Donors After Functional Assessment, Ex Vivo.
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
ADULT LUNG TRANSPLANTATION
Kaplan-Meier Survival By Diagnosis (Transplants: January 1990 – June 2009)

HALF-LIFE
- Alpha-1: 6.3 Years
- CF: 7.4 Years
- COPD: 5.3 Years
- IPF: 4.5 Years
- IPAH: 4.9 Years
- Sarcoidosis: 5.3 Years

Survival comparisons
All comparisons with Alpha-1 and CF are statistically significant at < 0.01

COPD vs. IPF: p < 0.0001

ADULT LUNG TRANSPLANTATION

1988-1994: 1/2-life = 4.7 Years; Conditional 1/2-life = 7.9 Years
1995-1999: 1/2-life = 4.8 Years; Conditional 1/2-life = 7.5 Years
2000-6/2009: 1/2-life = 5.8 Years; Conditional 1/2-life = 8.8 Years

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