Lung Diseases and Criteria Leading to Transplant

Roger F. Johnson, MD, FCCP
Pulmonary and Critical Care Medicine
St. Vincent Evansville Medical Center
Evansville, Indiana

Disclosures
• I have no conflicts of interest related to this topic
• While I often refer patients for lung transplant and manage advanced lung disease, I do not practice lung transplant medicine
• I have received honoraria from the following companies:
  – Bayer (Pulmonary hypertension)
  – Gilead (Pulmonary hypertension)
  – Genentech (Idiopathic pulmonary fibrosis)
  – AstraZeneca (COPD)
  – Pinnacle Biologics (Photodynamic therapy for lung cancer)

Objectives
• Understand general criteria for patient selection for lung transplantation
• Discuss absolute and relative contraindications for lung transplantation
• Understand how previous surgery and treatment for pneumothorax affects a patient’s candidacy for lung transplantation
• Understand disease-specific indications for lung transplantation
• Discuss the Lung Allocation Score (LAS)
• Discuss various statistics related to lung transplantation
• Discuss decision making related to selection of single versus double lung transplantation
Indications for Referral
Is a Lung Transplant Indicated?

Would a lung transplant be beneficial?
• Survival benefit?
• Quality of life benefit?

Can the patient tolerate the transplant surgery?
• Single v. bilateral?
• Underlying comorbidities?
• Age
• Frailty
• CAD, CRI
• DM, HTN...

General Criteria
• Patients with chronic, end stage lung disease who meet all of 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 there is adequate graft function

Absolute Contraindications
• Recent history of malignancy. Generally 5 year disease-free interval is required
• Untreatable significant dysfunction of another major organ system (e.g. heart, liver, kidney, brain) unless combined organ transplantation can be performed
• Uncorrected atherosclerotic disease with suspected or confirmed end-organ ischemia or dysfunction and/or coronary artery disease not amenable to revascularization
• Acute medical instability, including but not limited to acute sepsis, myocardial infarction, liver failure
Absolute Contraindications

- Uncorrectable bleeding diathesis
- Chronic infection with highly virulent and/or resistant microbes that are poorly controlled pre-transplant
- Evidence of Mycobacterium tuberculosis infection
- Significant chest wall or spinal deformity expected to cause severe restriction after transplantation
- Class II or III obesity \((\text{BMI} \geq 35.0 \text{ kg/m}^2)\)
- Current non-adherence to medical therapy or history of repeated or prolonged episodes of non-adherence to medical therapy that are perceived to increase the risk of non-adherence after transplantation

J Heart Lung Transplant 2015;34:1-15

Relative Contraindications

- Age > 65 in association with low physiologic reserve and/or other relative contraindications
- Class I obesity \((\text{BMI} 30.0 – 34.9 \text{ kg/m}^2)\), particularly truncal obesity
- Progressive or severe malnutrition
- Severe, symptomatic osteoporosis
- Extensive prior chest surgery with lung resection
- Mechanical ventilation or ECLS
- Colonization or infection with highly resistant or highly virulent bacteria, fungi, and certain strains of mycobacteria (chronic extrapulmonary infection expected to worsen after transplantation)

J Heart Lung Transplant 2015;34:1-15
Relative Contraindications

• Lung transplantation can be considered in patients with hepatitis B or C in those patients without significant clinical, radiographic, or biochemical signs of cirrhosis or portal hypertension and who are stable on appropriate therapy

• Lung transplantation can be considered in patients with HIV in those patients with controlled disease with undetectable HIV RNA and compliant on combined antiretroviral therapy. Candidates should have no current AIDS-defining illness

J Heart Lung Transplant 2015;34:1-15

Relative Contraindications

• Infection with Burkholderia cenocepacia, Burkholderia gladioli, and multidrug resistant Mycobacterium abscessus if the infection is sufficiently treated preoperatively and there is reasonable expectation for adequate control postoperatively

• Atherosclerotic disease burden sufficient to put the patient at risk for end-organ disease after lung transplantation

• In patients with CAD, patients may be candidates for percutaneous intervention, CABG preoperatively or CABG combined with lung transplantation

• Preoperative evaluation, degree of coronary artery disease deemed acceptable, and type of stent used (bare metal vs. DES) vary among transplant centers

J Heart Lung Transplant 2015;34:1-15

Relative Contraindications

• 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, and GERD should be optimally treated before transplantation

J Heart Lung Transplant 2015;34:1-15
Previous Surgery

- Previous surgery is not a contraindication to lung transplantation
- Pleurodesis is most troublesome, but also is not a contraindication
- Pneumothorax in patients who may become future transplant candidates should be treated with the most effective immediate management. Management strategy is unlikely to affect future acceptance for transplantation
- Higher rates of bleeding, reexploration, and renal dysfunction are expected in patients with previous chest procedures. This may be a function of longer cardiopulmonary bypass times

Timing of referral for Lung Tplx

- The evaluation process for transplantation is complex and time consuming
- Risk of worsening lung disease and overall health
  - Patient may become critically ill and the need for transplantation becomes urgent.
- Patients with a progressive lung disease should be referred to a transplant center when they are still able to undergo evaluation to determine the potential risks and benefits of lung transplantation in their case.
  - Early referral may identify modifiable risk factors that would influence a patient’s candidacy for transplantation or their outcome after transplantation.
- Factors that are timing restrictive include obesity, deconditioning, vaccination schedules, treatment of CAD

Slide Courtesy of Dr. David Roe Indiana University Lung Transplant Program
**Disease-Specific Indications**

**Timing of Referral: ILD**

- Histopathologic or radiographic evidence of usual interstitial pneumonitis (UIP) or fibrosing non-specific interstitial pneumonitis (NSIP), regardless of lung function.
- Abnormal lung function: forced vital capacity (FVC) <80% predicted or diffusion capacity of the lung for carbon monoxide (DLCO) <40% predicted.
- Any dyspnea or functional limitation attributable to lung disease.
- Any oxygen requirement, even if only during exertion.
- For inflammatory interstitial lung disease (ILD), failure to improve dyspnea, oxygen requirement, and/or lung function after a clinically indicated trial of medical therapy.

*J Heart Lung Transplant 2015;34:1-15*

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**Disease-Specific Indications**

**Timing of Referral: Cystic Fibrosis**

- FEV1 that has fallen to 30% or a patient with advanced disease with a rapidly falling FEV1 despite optimal therapy (particularly in a female patient), infected with non-tuberculous mycobacterial (NTM) disease or *Burkholderia cepacia* complex, and/or with diabetes.
- A 6-minute walk distance <400 m.
- Development of pulmonary hypertension in the absence of a hypoxic exacerbation (as defined by a systolic pulmonary arterial pressure (PAP) >35 mm Hg on echocardiography or mean PAP >25 mm Hg measured by right heart catheterization).

*J Heart Lung Transplant 2015;34:1-15*

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**Disease-Specific Indications**

**Timing of Referral: Cystic Fibrosis**

- Clinical decline characterized by increasing frequency of exacerbations associated with any of the following:
  - An episode of acute respiratory failure requiring non-invasive ventilation.
  - Increasing antibiotic resistance and poor clinical recovery from exacerbations.
  - Worsening nutritional status despite supplementation.
  - Pneumothorax.
  - Life-threatening hemoptysis despite bronchial emobilization.

*J Heart Lung Transplant 2015;34:1-15*
Disease-Specific Indications
Timing of Referral: COPD

- Disease is progressive, despite maximal treatment including medication, pulmonary rehabilitation, and oxygen therapy.
- Patient is not a candidate for endoscopic or surgical LVRS. Simultaneous referral of patients with COPD for both lung transplant and LVRS evaluation is appropriate.
- BODE index of 5 to 6.
- \( \text{PaCO}_2 >50 \text{ mm Hg or 6.6 kPa and/or PaO}_2 <60 \text{ mm Hg or 8 kPa.} \)
- \( \text{FEV}_1 <25\% \text{ predicted.} \)

J Heart Lung Transplant 2015;34:1-15

Disease-Specific Indications
Timing of Referral: Pulmonary Vascular Disease

- NYHA Functional Class III or IV symptoms during escalating therapy.
- Rapidly progressive disease (assuming weight and rehabilitation concerns not present).
- Use of parenteral targeted pulmonary arterial hypertension (PAH) therapy regardless of symptoms or NYHA Functional Class.
- Known or suspected pulmonary veno-occlusive disease (PVOD) or pulmonary capillary hemangiomatosis.

J Heart Lung Transplant 2015;34:1-15

Lung Allocation Score (LAS)

- As of May 2005, each lung transplant candidate is assigned a Lung Allocation Score (LAS).
- The LAS is between 0-100
- The LAS was designed to facilitate allocation of the limited supply of donor organs to patients with more urgent need
- Despite the implementation of the LAS, up to 20% of patients annually will either be inactivated or die before an adequate donor becomes available
- Donor availability has not kept up with the increased number of patients in need of lung transplantation

J Pulmonar Respirat Med 2012;2:2
Lung Allocation Score (LAS)

• Overall median wait time for lung transplantation is less than 6 months
• Patients with LAS of at least 50 have a median wait time of about 1 month
• Between 2005 and 2012, there has been a 58% increase in patients with LAS of 35 or greater

J Pulmonar Respirat Med 2012:2:2

Lung Allocation Score (LAS)

• In the United States, the lung allocation policy prioritizes lung transplant candidates for lung offers by assigning them a LAS
• The LAS is used to prioritize waiting list candidates based on a combination of waitlist urgency and post-transplant survival
  – Waitlist urgency is what is expected to happen to a candidate, given his or her characteristics, in the next year if a transplant is not received
  – Post-transplant survival is what is expected to happen to a candidate, given his or her characteristics, in the first year after transplant if a transplant is received

UNOS. A Guide to Calculating the Lung Allocation Score

Lung Allocation Score (LAS)

• Calculating the LAS involves all of these very complex steps:
  – Calculating the waiting list survival probability during the next year
  – Calculate the waitlist urgency measure
  – Calculate the post-transplant survival probability during the first post-transplant year
  – Calculate the post-transplant survival measure
  – Calculate the raw allocation score
  – Normalize the raw allocation score to obtain the LAS

UNOS. A Guide to Calculating the Lung Allocation Score
Lung Allocation Score

Part 1: Post transplant survival
- FVC
- PCWP ≥20
- Continuous mechanical ventilation
- Age
- Serum creatinine
- NYHA Functional class
- Diagnosis

Part 2: Waiting list urgency
- FVC
- S-PAP, m-PAP, PCWP
- Suppl.O2 required at rest
- Age
- BMI
- Diabetes
- Functional status
- Six-minute walk distance
- Continuous mech. ventilation
- Diagnosis
- pCO2

Transplant benefit = post transplant survival - waitlist survival.
- The raw allocation score = transplant benefit (days) - waitlist survival (days).
- The lung allocation score is derived by normalizing the raw allocation score to a range of 0 to 100.

Selection of Donor Lungs
- Extended donor criteria can be used, depending on patient acuity, which can increase the donor pool and shortening waitlist times:
  - Donor age > 55
  - PaO2:FiO2 ratio < 300 mmHg
  - Abnormal chest radiograph
  - Donor tobacco use for >20 years
  - Evidence of aspiration
  - Presence of purulent secretions on bronchoscopy of positive gram stain on lavage
  - Chest trauma or history of cardiopulmonary surgery

Other Factors Regarding Selection of Donor Lungs
- Donor and recipient size matching is important for adequate function of the transplanted organ as well as survival
- Donor and recipient ABO blood types and HLA compatibility (presence of panel reactive antibodies, PRA)
- Patients with high PRA, especially >25%, have increased 30 day and overall mortality
Adult Lung Transplants
Number of Transplants by Year and Procedure Type

**Note:** This figure includes only the adult lung transplants that are reported to the International Society for Heart and Lung Transplantation (ISHLT) Registry. As such, this should not be construed as representing changes in the number of adult lung transplants performed worldwide.

**Diagnosis**

- **COPD**
- **IP**
- **IIP**
- **CF**
- **ILD**
- **A1ATD**
- **Retransplant**
- **Non-CF bronchiectasis**
- **Sarcoidosis**
- **Pharm. IWP**
- **Lung fibrosis**
- **CTD**
- **Cancer**
- **Other**

**Procedure Type within Indication, by Year**

- **Bilateral/Double Lung Transplant**
- **Single Lung Transplant**
Adult Lung Transplants
Kaplan-Meier Survival by Procedure Type for Primary Transplant Recipients (Transplants: January 1990 – June 2015)

Median survival (years):
- Double Lung: 7.4; Conditional: 9.9
- Single Lung: 4.6; Conditional: 6.4

p<0.0001

Adult Lung Transplants

Median survival (years):
- 1990-1998: 4.2; Conditional: 7.1
- 1990-2008: 6.1; Conditional: 8.5
- 2009-6/2015: NA; Conditional: NA

p<0.0001

Adult Lung Transplants
Kaplan-Meier Survival by Diagnosis (Transplants: January 1990 – June 2015)

Median survival (years):
- AATD: 6.7; CF: 9.2; COPD: 5.8; IP: 4.6; ILD-not IP: 6.0; Retransplant: 2.9

All pairwise comparisons were significant at p < 0.05 except AATD vs. ILD-not IP and COPD vs. ILD-not IP.
Overall (N=17,058)
18-34 (N=2,119)
35-49 (N=2,553)
50-59 (N=4,985)
60-65 (N=4,608)
66+ (N=2,793)

Female (N=7,133)
Male (N=9,925)

% experiencing rejection within 1 year

Analysis is limited to patients who were alive at the time of the follow-up.

No rejection = Recipient had (1) no acute rejection episodes and (2) was reported either as not hospitalized for rejection or did not receive anti-rejection agents.

2017 JHLT. 2017 Oct; 36(10): 1037-1079

Functional and Employment Status and Rehospitalization Post Transplant

Adult Lung Transplants
Percentage Experiencing Any Rejection between Discharge and 1-Year Follow-Up (Follow-ups: July 2004 – June 2016)

No pair-wise comparisons were significant at < 0.05 except 18-34 vs. all other age groups.

Functional Status of Surviving Recipients (Follow-ups: January 2009 – June 2016)

1 Year (N = 11,203) 2 Year (N = 9,348) 3 Year (N = 7,879)
Adult Lung Transplants Surviving Recipients Working Post-Transplant
(Follow-ups: January 2009 – June 2016)

Adult Lung Transplants Rehospitalization Post-Transplant of Surviving Recipients
(Follow-ups: January 2009 – June 2016)

Single vs Bilateral/Double Lung Transplant

- The subject of a great deal of debate
- Short and long term outcomes are to be considered
- Individual and societal benefits also must be considered
- SLT maximizes benefit to society by transplanting 2 candidates per donor
- DLT maximizes benefit to the individual
- No high quality evidence comparing these 2 approaches
- Practice patterns are often institution specific

**Single vs Bilateral/Double Lung Transplant**

<table>
<thead>
<tr>
<th>Outcome parameter</th>
<th>Advantage SLT</th>
<th>Advantage BLT</th>
</tr>
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<tbody>
<tr>
<td>Duration of operation</td>
<td>--</td>
<td>--</td>
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<tr>
<td>ICU and hospital stay</td>
<td>--</td>
<td>--</td>
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<tr>
<td>Early mortality</td>
<td>--</td>
<td>--</td>
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<tr>
<td>PUL improvement with ILD</td>
<td>--</td>
<td>+</td>
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<tr>
<td>QOL measures</td>
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<tr>
<td>Delay from VAD</td>
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<td>+</td>
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<tr>
<td>Long-term survival</td>
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<td>+</td>
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<tr>
<td>Relative cost-effectiveness (individual perspective)</td>
<td>+</td>
<td>+</td>
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<tr>
<td>Maximal societal benefit</td>
<td>--</td>
<td>+</td>
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<tr>
<td>High risk recipient</td>
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**p<0.0001**

Diagnosis: AATD

**p<0.0001**
Kaplan-Meier Survival by Procedure Type

Diagnosis: COPD

p<0.0001

Diagnosis: IIP

p<0.0001

Diagnosis: ILD - not IIP

p<0.0001
Indications for Referral
Is a Lung Transplant Indicated?

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Thank you for your attention!!!